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Glucagon-like Peptide-1 Receptor Agonists as Novel Pharmacotherapies for Nicotine Dependence

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1. PROTOCOL

1.1. Full Title
Glucagon-like Peptide-1 Receptor Agonists as Novel Pharmacotherapies for Nicotine Dependence

1.2. Short Title
Daily Liraglutide for Nicotine Dependence

1.3. Brief Description
This clinical research trial examines the effects of the GLP-1 receptor agonist liraglutide on smoking behavior, food intake, and weight gain. In this double-blind, placebo-controlled, parallel arm pilot study, overweight and obese smokers (N=40; 20 female and 20 male) will be randomized to 32 weeks of liraglutide or placebo and undergo 8 sessions of smoking cessation behavioral counseling. Outcomes are smoking abstinence and weight change.

2. INTRODUCTION

2.1. Background
Tobacco use and obesity are the two leading causes of preventable deaths (1). A growing literature indicates that common neurobiological substrates mediate drug addiction and obesity (2, 3). Therefore, it is not surprising that during smoking abstinence, highly palatable food may serve as a substitute reinforcer ultimately leading to increased body weight gain. Importantly, post-cessation weight gain (PCWG) can deter a quit attempt, precipitate smoking relapse, and contribute to health issues related to excess body weight (4-8). The majority of weight gain occurs within 3-6 months of quitting smoking (9, 10) and many individuals maintain this increased weight 5 to 20 years post-cessation (11-13). Although there is substantial variability in the amount of weight gained, individuals who successfully quit smoking gain an average of 4.2 kg, with estimates ranging from 2.5 kg to 8.6 kg, at 6-month follow-up (9, 10, 14, 15). Weight gain after smoking cessation contributes to increased risk of obesity (16), type II diabetes mellitus (17) and hypertension (18), as well as reducing the improvement in lung function conferred by smoking cessation (19). Moreover, overweight or obese smokers comprise 70% of treatment-seeking smokers, gain the most weight, and are the least accepting of PCWG (20-23). Thus, post-cessation weight gain is a significant clinical problem (16, 24, 25). Unfortunately, current pharmacological interventions to reduce post-cessation weight gain are not very effective (6).

While weight gain is often cited as a primary reason for smoking relapse (16, 25), there is a significant gap in our understanding of the biobehavioral mechanisms linking smoking cessation and overeating. Recent evidence indicates that glucagon-like peptide-1 (GLP-1) regulates the rewarding effects of nicotine (26). These effects are mediated, in part, by reduced dopamine signaling in the nucleus accumbens, a key brain region known to regulate the reinforcing effects of both drugs of abuse and palatable foods (26-28). Indeed, activation of GLP-1 receptors in the VTA, a brain region that sends dopaminergic projections to the nucleus accumbens, reduces both drug intake and consumption of palatable food (29, 30). Based on the ability of GLP-1 receptor agonists to reduce drug and food intake, it is plausible that targeting GLP-1 receptor signaling may be an effective strategy toward reducing withdrawal-induced weight gain in abstinent smokers.

We have recently developed a novel animal model of nicotine withdrawal-induced hyperphagia and body weight gain in order to gain an improved understanding of the molecular and behavioral mechanisms underlying increased food intake and body weight gain during nicotine withdrawal. Our pilot data provide strong empirical rationale for the proposed study by establishing an animal model of withdrawal-induced hyperphagia and body weight gain following voluntary nicotine self-administration. This withdrawal phenotype was evident only in rats given ad libitum access to a highly palatable diet during withdrawal as parallel studies using a normal chow diet did not produce hyperphagia or changes in body weight during nicotine withdrawal (data not shown). Collectively, these results are consistent with human laboratory studies indicating that nicotine withdrawal is associated with

increased consumption of highly palatable foods and body weight (31-33). The translational implications of studying this behavioral phenotype are clear and significant and include: 1) informing clinical approaches to treating weight gain during smoking abstinence, 2) identifying potential biomarkers associated with nicotine addiction, and 3) addressing two significant public health concerns.

GLP-1 receptor ligands are currently FDA-approved for the treatment of type II diabetes mellitus (34, 35) and obesity (36). Re-purposing an existing FDA-approved treatment that has been "de-risked" (i.e., previously shown to be safe) in numerous clinical trials (37-40) removes a key barrier for drug development and reduces the resources required to bring new drugs to market (41, 42).

Our promising preclinical data, combined with evidence that GLP-1 receptor agonists are effective treatments for obesity, suggest that GLP-1 receptor ligands could be re-purposed for attenuating nicotine withdrawal-induced bodyweight gain, thereby improving smoking cessation rates. Specifically, we will examine the effects of the GLP-1 receptor agonist liraglutide on smoking behavior as well as food intake and body weight gain during abstinence.

3. STUDY OBJECTIVES

3.1. Primary Objective

The purpose of this study is to examine the effects of the GLP-1 receptor agonist liraglutide on smoking cessation at 12 and 26 weeks post Target Quit Date (TQD) in treatment-seeking daily cigarette smokers.

Aim 1: Determine the effects of the GLP-1 receptor agonist liraglutide on smoking behavior in daily cigarette smokers during a quit attempt.

Hypothesis 1: Compared to placebo, liraglutide will improve abstinence rates (i.e., 7-day point prevalence) at 12- and 26-week post TQD follow-up.

3.2. Secondary Objective

Secondarily, we will examine the effects of liraglutide on body weight gain at 12 and 26 weeks post Target Quit Date (TQD) in treatment-seeking daily cigarette smokers, relative to baseline (Week 1).

Aim 2: Evaluate the effects of the GLP-1 receptor agonist liraglutide on body weight gain in daily cigarette smokers during a quit attempt.

Hypothesis 2: Compared to placebo, liraglutide will attenuate body weight gain at 12- and 26-week post TQD follow-up.

3.3. Exploratory Aims

We will explore the mechanisms by which liraglutide reduces body weight gain and promotes smoking cessation. Specifically, we will assess food intake (i.e., total calories consumed) and the rewarding value of food (Week 0 vs. Week 5) and whether these changes are correlated with weight gain and quit rates.

4. STUDY DESIGN

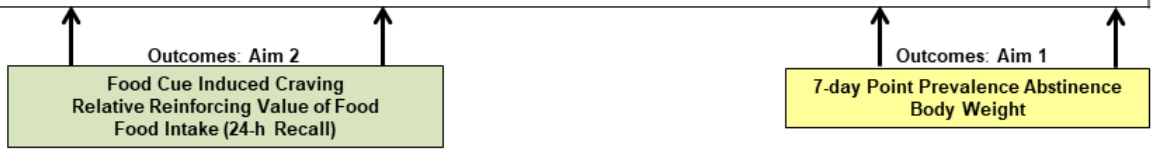
4.1. General Design

This is a randomized, double-blind, placebo-controlled, parallel arm pilot study with one between-subjects factor of medication group (liraglutide vs. placebo). After confirming eligibility during the Intake Visit (Week -1), participants will complete a 32-week study, which is divided into two phases: a 5-week Run-up Pre-Quit Phase (aka Pre-Quit period) and a 6-month Cessation Follow-up Phase (aka Monitoring period). Participants will attend a Baseline visit/Lab session 1 (Week 1) to assess baseline smoking rate, body weight, food intake (measured via three days of 24-hr food recalls), and food craving. At Lab Visit Week 1, subjects will be randomized to one of two groups (liraglutide or placebo; 1:1 ratio). The dosing regimen, which follows FDA guidelines will begin at 0.6 mg and increase weekly by 0.6 mg until the recommended dose of 3 mg is reached (Weeks 1 through 5) and will continue at the 3 mg dose through the end of the study (Week 32). Side effects and smoking rate will be assessed at Weeks 2, 3, and 4 (Figure 1). During Week 5, subjects will complete Lab session 2 to assess food intake and food craving during nicotine withdrawal. At the Week 5 visit, participants will receive a 1-hour standard behavioral counseling session to prepare them for the TQD (typically one week later). Participants will receive smoking cessation counseling at Weeks 6 (TQD), 7, 8, 10, 12, 18, and 26 (a total of 8 sessions) (43). Participants will attend Monitoring Visits at Weeks 18 and 32 [EOT] to assess biochemical verification of smoking abstinence, body weight, and side effects.

Figure 1. Study Design and Visits

Phase		Run-up Pre-Quit Phase					Cessation Follow-up Monitoring Phase									
Week		1	2	3	4	5	6	7	8	10	12	14	18	22	26	32
							TQD						12 weeks post-TQD			EOT
Medication Condition		L or P (Day 1)	Liraglutide or Placebo			L or P	Liraglutide or Placebo									
Activity	Intake	Baseline/ Lab 1	PQV	PQV	PQV	Lab 2[1]	MV[1]	MV[1]	MV[1]	MV[1]	MV[1]	MV	MV[1]	MV	MV[1]	MV
State	SAU	SAU	SAU	SAU	SAU	SAU	Abstain									

Smoking rate, CO, side effects, and body weight will be assessed at every visit. [1] Behavioral counseling session
SAU = Smoking as Usual; PQV = Pre-Quit Visit; MV = Monitoring Visit; TQD=Target Quit Date; EOT = End of Treatment



Rationale for Study Design

An improved understanding and targeting of the mechanisms that underlie smoking relapse is the most efficient path for developing more effective treatment approaches (44-46). Our well-validated paradigm (47-51) addresses this issue in two ways. First, it allows for a naturalistic evaluation of changes in smoking behavior during the drug run-up period. For example, it is possible that liraglutide has effects on smoking behavior at a dose lower than the 3 mg dose indicated for weight management (i.e., smokers in the liraglutide may reduce smoking prior to the target quit day). Thus, by asking smokers to simply follow their urges to smoke, important information will be gained from this study. Moreover, there is evidence that longer pre-treatment periods are effective strategies for improving the efficacy of pharmacotherapy for smoking cessation (138, 139). Second, and most importantly, we will capitalize on these data to evaluate the degree to which changes in feeding behavior in the liraglutide group account for changes in smoking behavior. Elucidating the mechanisms that underlie relapse will both advance knowledge and provide new targets for subsequent population-specific treatment development (46).

We chose a six-month follow-up duration for several reasons. First, six months meets the recommendations for smoking cessation trials (52), treatment guidelines (53), and the inclusion criteria for systematic reviews and meta-analyses (54). Second, several studies indicate that, compared to placebo, liraglutide produces significant changes in body weight following 6 months of treatment (55, 56). Although post-cessation weight gain can continue up to 12 months after quitting smoking (57, 58), the majority of weight gain occurs within 3-6 months of quitting (9, 10) and many individuals maintain this increased weight 5 to 20 years post-cessation (11-13) suggesting that longer

term follow-ups may not provide substantial new information. Smoking will be measured throughout the trial via timeline follow-back and biochemically verified via CO. Body weight will be measured at week 1, week 5, week 18, and week 32. If the participant reports smoking abstinence at week 7, the participant will be mailed an iCO Smokerlyzer device to measure their CO levels at weeks 7, 8, 10, 12, 14, 22, and 26. This design will allow us to capture body weight changes in the most critical time period after quitting smoking. Assessment of food intake at Baseline (week 1), week 5, week 18 (12 weeks post-TQD), and week 32 (26 weeks post-TQD) will allow us to capture increases in food intake that initially drive and subsequently sustain weight gain (59-61).

Randomization and Blinding

Neither the investigators nor study staff working with participants will have access to randomization status. Only the Data Manager will know which study group participants were assigned to. Participants will be assigned to liraglutide or placebo using a 1:1 ratio. Study groups will be matched on sex, BMI, and nicotine dependence level.

Breaking of Blinded Codes

In the event that participants are prematurely discontinued from the study, it will be necessary to avoid breaking the blind whenever possible in order to protect the integrity of the study. If an emergency necessitates that the blind be broken, the PI, Study Physician, or Project Manager (on behalf of the PI/Study Physician) will contact the Data Manager and make an official request that the study blind be broken for the participant. The person breaking the code will record the date, time, and reason for breaking the blind in the CRFs. All codes will be stored for the duration of the research study.

4.2. Study Duration

Participants will be involved in study-related activities for approximately 8 months from initial eligibility assessment in the clinic through follow-up. A participant's length of time in the study may be affected by center or participant scheduling conflicts

Enrollment will begin in Month 3 of the project to allow for IRB approval, development of the Data Management System, and staff training. We estimate enrolling ~2-3 smokers per month over an 18-20 month recruitment period (Months 3-22). We estimate that 40 people will complete the study by Month 30, and that analyses and the final study report will be complete by Month 36.

5. CHARACTERISTICS OF THE STUDY POPULATION

5.1. Target Population

Adults (N=40; 20 female and 20 male) who have smoked cigarettes at least 10 times per day for the past 6 months (48, 62) will complete the study. We conservatively estimate a drop-out rate of 50% and will randomize 80 smokers to have 40 complete the study.

5.2. Accrual

To enroll 80 smokers, we will need to screen about 800 smokers (accounting for 10% eligibility). Over an 18-20 month period, we expect to screen ~40 smokers/month and enroll ~4 smokers/month, which is feasible based on our prior studies (51, 63). To maximize retention, we will: (a) schedule sessions at convenient times; (b) maintain close contact; and (c) provide compensation. All study procedures and visits will occur at the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) at the University of Pennsylvania in Philadelphia, PA.

5.3. Key Inclusion Criteria

Eligible subjects will be males and females:

1. 18 years of age or older who self-report smoking cigarettes (menthol and non-menthol) at least 10 times per day, on average, for the past 6 months.
2. Interested in quitting smoking (defined as "intend to quit within one month").

3. Body mass index (BMI) greater than or equal to 27 kg/m^2 with one weight-related comorbidity (e.g. high blood pressure, high cholesterol, dyslipidemia) or greater than or equal to 30 kg/m2 per the manufacturer label for weight management.
4. Women of childbearing potential (based on medical history) must consent to use a medically accepted method of birth control (e.g., condoms and spermicide, oral contraceptive, Depo-Provera injection, contraceptive patch, intrauterine device (IUD), tubal ligation) or agree to abstain from sexual intercourse during the time they are in the study.
5. Able to communicate (speak, read, and write) fluently in English.
6. Capable of giving written informed consent before any study-related activities, which includes compliance with the requirements and restrictions listed in the combined consent/HIPAA form.
7. If current or past diagnosis of bipolar disorder, eligible if:
    a. No psychotic features
    b. MADRS: total score less than 8 (past 4 weeks); suicidal item score less than 1 (past 4 weeks)
    c. Y-MRS: total score less than 8 (past 4 weeks); irritability, speech content, disruptive or aggressive behavior items score less than 3 (past 4 weeks)
    d. No psychiatric hospitalization or Emergency Room visits for psychiatric issues in the past 6 months
    e. No aggressive or violent acts or behavior in the past 6 months

5.4. Key Exclusion Criteria

Subjects who present with and/or self-report the following criteria will not be eligible to participate in the study.

Smoking Behavior:

1. Current enrollment in a smoking cessation program, or use of other smoking cessation medications (e.g. Chantix/varenicline, Zyban/bupropion, nicotine replacement therapy/gum/patch, etc.) in the last month or plans to do either in the next 2 months.
2. Daily use of chewing tobacco, snuff and/or snus, or electronic cigarettes.

Alcohol/Drug Use:

1. Self-report current alcohol consumption that exceeds 25 standard drinks/week over the past 6 months.
2. Current untreated and unstable diagnosis of severe substance use disorder (eligible if past use and/or if receiving treatment and stable for at least 30 days). Current untreated and unstable moderate substance use disorder requires Study Physician approval.
3. A positive urine drug screen for cocaine, methamphetamines, PCP, barbiturates, and/or ecstasy (MDMA).
    a. Participants believed to have a false-positive result on the drug screen may continue with the study with investigator approval.

Medical:

1. Females who self-report current pregnancy, planning a pregnancy during the study, currently breastfeeding/lactating, or not using adequate contraceptive measures. All female participants will undergo a urine pregnancy test at Intake and at every study visit. If the participant is unable to attend a monitoring visit in person, the urine pregnancy test would then be conducted during in-person visits at Intake, Weeks 1, 5, 18, and 32.
2. Current diagnosis of unstable and untreated major depression, as determined by self-report & MINI (eligible if stable for at least 30 days).
3. Current or past diagnosis of psychotic disorder, as determined by self-report or MINI. Mood Disorder with Psychotic Features determined by MINI requires PI approval for eligibility.
4. Suicide risk on the C-SSRS indicated by active suicidal ideation (within the past 30 days), any suicidal attempt within the past 2 years, or 2 or more lifetime suicidal attempts.
5. Self-reported kidney and/or liver disease or transplant.
6. Heart/Cardiovascular disease (e.g., angina, coronary heart disease, stroke, etc.) in the past 6 months.

7. Type-1 or type-2 diabetes (previously diagnosed or indicated by HbA1c level of 6.5% or higher).
8. Uncontrolled hypertension (BP systolic greater than 159 and/or diastolic greater than 99)*.
9. Personal or family history of medullary thyroid carcinoma (MTC).
10. Personal or family history of Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
11. History of pancreatitis.
12. History of gallbladder disease.
13. A blood glucose level less than 70 mg/dl at the Intake Visit.
14. Prior history, or plans, of surgical intervention for weight loss.
15. Hypersensitivity to liraglutide or any product components.
16. Current diagnosis of hyperthyroidism or hypothyroidism (requires thyroid function test review by SP to determine eligibility)
17. Recent weight loss (more than or equal to 5% body weight) in the past 3 months

* Participants presenting with SBP greater than 159 mmHg and/or DBP greater than 99 mmHg at the Intake visit will be instructed to sit quietly for 10 minutes. Then the participant will have a second blood pressure reading taken after a 10-minute period. If, after the second reading the SBP greater than 159 mmHg and the DBP greater than 99 mmHg, the individual will be instructed to sit comfortably for 10 minutes and then have a third blood pressure reading. If, after the third reading the SBP greater than 159 mmHg and the DBP greater than 99 mmHg, the individual will be ineligible to participate.

Medications:

1. Current or recent use (last 14 days) of weight loss medication, and/or use of medications known to impact weight (e.g. corticosteroids, excluding inhaled).

General Exclusion:

1. Current, anticipated, or pending enrollment in another research program over the next 2-3 months that could potentially affect subject safety and/or the study data/design as determined by the Principal Investigator and/or Study Physician.
2. Not planning to live in the area for the next 9 months.
3. Previous participation in this trial (i.e., previously randomized and started study medication).
4. Any impairment (physical and/or neurological) including visual or other impairment preventing ability to complete study tasks.
5. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator.

5.5. Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the study will be independent of the subject's work or school activities. Penn affiliates will be informed that their decision of whether to participate will not impact their standing with the institution.

5.6. Subject Recruitment

Subjects will be recruited from several sources including television, radio, newspaper advertisements, and from the Endocrinology and Metabolic Medicine Services at the Hospital of the University of Pennsylvania, Presbyterian Hospital, and Pennsylvania Hospital. Dr. Amaro will oversee the integration of this study into the clinics, ensuring access to participants and referring eligible individuals to this research study. Study brochures will be distributed in patient clinics, such as the Endocrinology and Metabolic Medicine Services overseen by Dr. Amaro, and at other

community locations and events.

After completing the necessary training and clinic clearances to access PennChart for participating UPHS clinics, Research Assistants (RAs) will review the electronic medical records to identify potential subjects on a weekly basis (each site has patient smoking status indicated on the record). Individual medical records will be evaluated for eligibility based on the inclusion and exclusion criteria for this study. Daily clinic schedules will be ascertained and RAs will approach patients prior to or after consultation or treatment at the clinic. In addition to in-clinic recruitment, RAs will contact potentially eligible patients (after EMR review) by telephone based on their clinic provider's specified research contact preference. Providers may choose one of the following contact options: 1) all patients identified as initially eligible may be contacted 2) all patient records identified as initially eligible will be sent to the provider via PennChart for review and approval prior to contact 3) all patient records identified as initially eligible may be sent to the provider, who assumes full responsibility and discretion regarding the research contact (no contact may be made by the research staff). Those patients deemed eligible for contact will be contacted by telephone. RAs will introduce the research study and the collaboration between the researchers, infectious disease clinic, and the patient's provider. After assessing the patient's interest, weight, and smoking status, the patient will then be provided with additional study information and an opportunity to assess his/her intake eligibility based on a screening questionnaire. Research Recruitment Best Practice Advisories (BPAs) will also be integrated into electronic medical record recruitment. BPAs are designed to fire passive alerts within PennChart at the point of care, notifying providers that a patient may be eligible for a specific study. This specific BPA will evaluate if a patient meets specific criteria associated with the trial and will present the provider with the option to indicate if a patient is interested in participating in the study or not. This BPA will only present if the patient meets the initial screening criteria based on smoking status and problem list diagnoses and will only present in specified departments. This indication of interest only serves to trigger a notification to study staff that a patient has met initial screen criteria and further follow-up is requested to determine eligibility of the patient. This alert is a passive alert and will not interrupt the provider's workflow, but will be listed in the same section as other clinically warranted BPAs.

Potential participants will complete an initial eligibility assessment online or by phone, reducing the likelihood that participants attend an Intake Visit only to learn that they are ineligible. In addition, the pre-screen assessment allows for the ascertainment of physician's clearance should the participant have a medical condition that affects safety with using liraglutide. If a potential participant cannot be reached by phone, RAs may send a text for the purposes of scheduling an initial eligibility screening phone call. This will help to reach potential participants who express interest in the study but do not answer phone calls from unrecognized numbers or do not regularly listen to voicemail messages. Texts will be sent from a central study account and not from the personal cellphones of any research staff. Participants who are interested/eligible at pre-screen will complete the Intake session with research staff. At this Intake session, participants will review and sign a combined informed consent and HIPAA authorization form, complete eligibility and baseline assessments, and be scheduled for their Lab Visit 1 (Week 1). Participants' eligibility will be confirmed by Dr. Ashare or a member of the study team.

<u>Referral Bonus Program</u>
Participants who achieve their final study visit (Week 32) will be given the opportunity to receive a small bonus for referring others to the study. If the person who is referred completes the initial eligibility screen, regardless of outcome, the study participant will be awarded $10 per referral, for a maximum of 2 referrals ($20).

5.7. Early Withdrawal of Subjects

Participation is voluntary and participants can withdraw from the study at any time. Study participants will be asked about the reason(s) for voluntary withdrawal (if applicable) and the presence of any AEs. AEs will be followed-up when appropriate. Participants who withdraw from the study will be instructed to return any unused study drug (if applicable).

Withdrawal Criteria

Participants may be withdrawn from the study for the following reasons:

1. Pregnancy or intention of becoming pregnant.
2. Applicable adverse event.
3. Severe non-compliance with study protocol/design, including missing a mandatory visit.
4. Any medical condition, illness, disorder, or concomitant medication that could compromise participant safety or performance, as determined by the Principal Investigator and/or Study Physician.
5. Intolerance of the 3mg dose of the study medication.

Replacement of Study Participants

Participants who withdraw from the study or fail to meet study requirements prior to completing Lab Visit 2 (Week 5) will be replaced to ensure that 40 participants complete the study. Per convention, participants who withdraw or are lost to follow-up during the Cessation Follow-up Phase will be included in the intent-to-treat analysis and coded as smokers. Based on our past research (65-67), we will enroll 40 more smokers to account for those unable to complete the study.

6. STUDY DRUG

6.1. Description

Liraglutide

Liraglutide 3.0 mg (Saxenda®) is an injectable medicine that may help some adults with excess weight (BMI ≥27) who also have weight-related medical problems or obesity (BMI ≥30) lose weight and keep the weight off. Liraglutide is approved by the U.S. Food and Drug Administration (FDA) for chronic weight management when combined with a reduced-calorie meal plan and physical activity. Liraglutide comes in a pre-filled pen and is self-injected one time per day into the abdomen, thigh, or upper arm area. Liraglutide belongs to a class of medications called glucagon-like peptide-1 (GLP-1) receptor agonists. The human body naturally produces glucagon-like peptide-1 (GLP-1), which helps regulate appetite. Liraglutide works like GLP-1. When activated by liraglutide, the GLP-1 receptor stimulates the release of insulin into the bloodstream. Evidence shows that liraglutide may reduce appetite.

Placebo

The placebo is an inactive substance that is designed to look like the study drug but contains no medication.

6.2. Treatment Regimen

The dosing regimen, which follows FDA guidelines and is documented to be safe and well-tolerated in prior clinical studies, will begin at 0.6 mg and increase weekly by 0.6 mg until the recommended dose of 3 mg is reached (Weeks 1 through 5) and will continue at the 3 mg dose through the end of the study (Week 32). Each pen contains 18mg of liraglutide and can be adjusted to any of the 5 doses (i.e., once the 3 mg dose is reached, the pen lasts 6 days). Thus, with the current dosing regimen, each participant will need approximately 34 pens to complete the study. If a participant does not tolerate an increased dose of study medication during dose escalation, dose escalation may be delayed for approximately one additional week.

6.3. Preparation and Packaging of Study Drug

Liraglutide (Saxenda®) 6mg/ml strength solution for subcutaneous injection and matched placebo pens will be manufactured and provided by Novo Nordisk. Study medication will be packed blinded and the packaging will be QA released by Clinical Supplies Novo Nordisk prior to distribution. The study medication and placebo pens will be shipped with a randomization list. Clinical Supplies Novo Nordisk will also supply a DFU (directions for use) that will be given to study participants along with the liraglutide/placebo pens.

6.4. Subject Compliance and Monitoring

Medication adherence data will be collected and recorded at every applicable time point. The research staff may collect used study medication pens, when possible, at in-person visits. Unused pens may be used to verify the medication adherence data. All discrepancies will be explored and recorded as appropriate. Adherence will be defined as greater than or equal to 80% compliance with the study regimen. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose. If more than 3 days have elapsed since the last dose, the Study Physician will be contacted to discuss whether it is necessary to withdraw the participant from the study or reinitiate liraglutide at 0.6 mg daily and follow the dose escalation schedule, which may reduce the occurrence of gastrointestinal symptoms associated with re-initiation of treatment.

6.5. Receiving, Storage, Dispensing, and Return

6.5.1. Receipt of Drug Supplies

The study drug supplier will ship liraglutide and the randomization list to the University of Pennsylvania Investigational Drug Service (IDS). Upon receipt of the study treatment supplies, an inventory must be performed and a proof of receipt filled out and signed by the person accepting the shipment. It is important that IDS staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study medication in a given shipment (active drug or placebo) will be documented in the study files maintained at IDS.

6.5.2. Storage of Study Drug

The IDS will store the medication per manufacturer guidelines. Specifically, prior to being dispensed to participants, liraglutide will be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC). It will not be stored in the freezer or directly adjacent to the refrigerator cooling element.

Participants will be told that after initial use of the pen, the pen can be stored for 30 days in a refrigerator (36°F to 46°F; 2°C to 8°C) or at room temperature (59°F to 86°F; 15°C to 30°C. Participants will be instructed to keep the pen cap on when not in use and that the pen should be protected from excessive heat and sunlight. In addition, participants will be instructed to always remove and safely discard the needle into a sharps container after each injection and store the pen without an injection needle attached.

6.5.3. Dispensing of Study Drug

Kits will be assigned and ordered from IDS as needed by the research staff and stored in a locked refrigerator at our center. Once the Study Physician (Dr. Anastassia Amaro) confirms eligibility, the subject will be assigned the next 3-digit number from the randomization list, and the prescription will be signed by either the SP or Nurse Practitioner. The randomization number encodes the treatment the participant will receive (liraglutide or placebo). The study medication will be dispensed using a unique Dispensing Unit Number (DUN) to ensure that the product supplied to each participant matches the treatment allocation. Participants who are ineligible or who do not enroll in the study will not receive study medication. The Data Manager will maintain a separate database linking the participant's study ID with the DUN. This database will only be accessible to the Data Manager. Due to the COVID-19 pandemic, procedures have been modified to allow for situations in which study staff are not able to pick up study medication and/or subjects are not able to attend their visit in-person and collect their study medication. The staff will work with IDS to determine the possibility of shipping the medication to the subject. Staff will confirm with the subject prior to shipment that they are able to receive deliveries and confirm their address.

6.5.4. Reconciliation and Return/Destruction of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug used, and drug remaining. Any returned and/or unused medication will be stored separately from used study medication. This reconciliation will be logged in the study database.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed, and dated by the research staff. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

7. STUDY PROCEDURES

7.1. Pre-Screening

Recruited subjects will complete an initial eligibility screening online via REDCap or over the telephone. This pre-screening reduces the likelihood that participants attend an Intake Visit only to learn that they are ineligible and/or to allow us to ascertain physician's clearance should the participant have a medical condition that requires approval. Participants who complete this pre-screening and are deemed potentially eligible will be invited to attend an Intake Visit. The Intake Visit must occur within 60 days of the initial eligibility screening or the participant will have to be re-screened.

7.2. In-Center Visits

7.2.1. Intake Visit

The purpose of this visit is to determine if participants are eligible to participate in the study. This visit will last approximately 3 hours if conducted entirely in-person. Participants may be asked to complete the consenting process remotely. Subjects may be contacted via Blue Jeans (HIPAA-compliant) for a videoconference or by phone. Staff will review the consent form and answer all questions. Staff will then administer a comprehension questionnaire and review incorrect answers as needed. Subjects who are unable to provide an electronic signature may be mailed a physical version of the consent that must be mailed back to us prior to continuing with the Intake tasks. During this visit, participants will:

- Provide a urine sample (at least 30ml [two tablespoons]) for drug and (if applicable) pregnancy tests. If participants test positive for cocaine, methamphetamines, PCP, barbiturates, and/or ecstasy (MDMA) may not be eligible to participate in this study. Results from these tests are used for research purposes only. They will not be shared with the participants and will not be placed in the participant's electronic medical record. The participant will be informed of his/her eligibility status after testing, but specific results will not be shared. Some OTC and other non-exclusionary medications are known to cause false-positives on urine drug screens. If a participant is believed to have a false-positive result on the urine drug screen, the participant may continue in the study with investigator approval. Urine samples will be discarded after testing.
- **Female participants only:** If the result of the pregnancy test is positive, the participant will not be eligible to participate in this study.
- Provide a breath sample for a carbon monoxide (CO) assessment to confirm smoking status. Carbon monoxide is a poisonous gas that comprises less than 1% of the air we breathe and is also produced through smoking a cigarette.
- Complete brief psychiatric assessments called the 'MINI' interview, 'C-SSRS', and 'CES-D' questionnaire. During these assessments, research staff will ask participants about any current and past depressed mood symptoms as well as other psychiatric symptoms.*
- Complete a medical history form with a member of the research team and provide information on medications participants are currently taking or recently discontinued.*
- Have height, weight, blood pressure, and heart rate measured.
- Complete a brief physical examination led by a medical professional.
- Have blood sugar measured via a finger prick and a handheld glucose monitor.
- Provide a 12.5mL blood sample (less than 3 teaspoons) that will be used to confirm participants do not have diabetes or any undiagnosed kidney or liver problems.

- Fill out questionnaires electronically via REDCap or on paper. These questionnaires ask about demographics, smoking history and behavior, and alcohol use and will take up to 45 minutes to complete.*
- Complete a computerized lab task by rating how appetizing the participant finds a set of pictures of food.
- Schedule a study track and next in-person visit.
- Schedule the dates and times of the first three 24-hour dietary recalls, which will be completed prior to Laboratory Visit 1 (Week 1).

* Subjects may be asked to complete these procedures remotely using REDCap or with study staff by Blue Jeans (HIPAA-compliant) or by phone to limit the amount of time subjects spend at the center.

During participants' entire participation in this study, we ask that they:

- NOT use any forms of nicotine replacement therapy (e.g., nicotine gum, nicotine spray, cigars, e-cigarettes, any type of vaped nicotine, lozenge, etc.).
- NOT use any study prohibited medications or recreational drugs as listed above.
- Notify us if they are prescribed a new medication (prior to taking first dose if possible).
- NOT participate in any other quit smoking programs and/or quit smoking research studies while they are enrolled in this study.
- **Female participants only:** Notify us immediately if they become pregnant. If participants become pregnant, they will NOT be able to continue in the study.
- Notify the research staff about any medical concerns and/or symptoms.
- Attend ALL study visits as scheduled.
- Follow ALL study instructions as directed.

7.2.2. Laboratory Visits

During the Pre-Quit period of the study, participants will attend two in-person laboratory visits at our center (Weeks 1 & 5 [+/- 2 days]). Subjects may be asked to complete some of these procedures remotely using Blue Jeans (HIPAA-compliant) or by phone to limit the amount of time subjects spend at the center. Participants will be asked NOT to eat anything for at least one hour before these visits. During these visits, participants will:

- Provide a urine sample (at least 30ml [two tablespoons]) for drug and (if applicable) pregnancy tests. If participants test positive for cocaine, methamphetamines, PCP, barbiturates, and/or ecstasy (MDMA), they may not be able to continue in the study. Results from these tests are used for research purposes only. They will not be shared with the participant and will not be placed in their electronic medical record. The participant will be informed of his/her eligibility status after testing, but specific results will not be shared. Some OTC and other non-exclusionary medications are known to cause false-positives on urine drug screens. If a participant is believed to have a false-positive result on the urine drug screen, the participant may continue in the study with investigator approval. Urine samples will be discarded after testing.
- **Female participants only:** If the result of the pregnancy test is positive, the participant will not be able to continue in the study.
- Provide a breath sample for a carbon monoxide (CO) assessment.
- Review current medications with a member of the research team and provide information on any new medications the participant may have started.
- Have weight, blood pressure, and heart rate measured.
- Have blood sugar measured via a finger prick and a handheld glucose monitor.
- Provide an 18.5mL blood sample (less than 4 teaspoons) that will be used to analyze exploratory cardiovascular risk markers.
- Fill out questionnaires, including a symptoms evaluation checklist, electronically via REDCap or on paper. These questionnaires will take up to 30 minutes to complete.
- Complete a series of food-related computer tasks (~30 minutes).

- At Lab Visit Week 1, participants will receive their first batch of study medication pens (liraglutide or placebo), a supply of one-time use needles, and a small sharps container. Participants will be trained by a medical professional on proper injection techniques. Training reduces the risk of administration errors such as needle sticks and incomplete dosing. Participants will be given Instructions for Use with complete administration instructions and illustrations to refer to when they administer the medication at home. Participants will also be trained on storing the study medication, disposing of used needles, and returning used medication pens and sharps containers to our center. Additional study medication pens (liraglutide or placebo) will be given/mailed to participants at Weeks 5, 7, 10, 12, 14, 18, 22, & 26. Participants will receive 1 box of study medication (3 pens) at Weeks 1, 5, 7, 10, 12 & 18 and 2 boxes of study medication (6 pens) at weeks 14, 22, & 26.

Laboratory Visit 2 only:

- Provide information on medication adherence and return used medication pens.
- Receive the first smoking cessation counseling session (~1 hour). All participants will take part in the same smoking cessation counseling program. This first counseling session will help prepare participants for their upcoming target quit date, which will occur the following week (Week 6). Counseling sessions may be audio-taped to ensure that treatment is consistent for all participants. Audio recordings will be saved on password-protected computers and deleted at the end of the study.

7.2.3. Pre-Quit Clinic Visits

During the Pre-Quit period of the study, participants will complete four sessions in between each lab session (Weeks 2, 3, & 4 [+/- 2 days]). These visits will last approximately 30 minutes. During these visits, participants will:

- **Female participants only:** Provide a urine sample for a pregnancy test. If the result of the pregnancy test is positive, the participant will not be able to continue in the study. Urine samples will be discarded after testing.**
- Provide a breath sample for a carbon monoxide (CO) assessment.**
- Have weight, blood pressure, and heart rate measured. **
- Review current medications with a member of the research team and provide information on any new medications the participant may have started.
- Have blood sugar measured via a finger prick and a handheld glucose monitor.**
- Fill out questionnaires, including a symptoms evaluation checklist, electronically via REDCap or on paper. These questionnaires will take up to 10 minutes to complete.
- Provide information on medication adherence and return used medication pens.

Week 4 Pre-Quit Clinic Visit only:

- Schedule the dates and times of the next three 24-hour dietary recalls, which will be completed prior to Laboratory Visit 2 (Week 5).

** Procedure only completed if session is completed in-person.

7.2.4. Monitoring Clinic Visits

During the Monitoring period of the study, participants will complete ten clinic visits at our center or over the phone (Weeks 6, 7, 8, 10, 12, 14 [+/- 2 days] and Weeks 18, 22, 26, & 32 [+/- 7 days]). Weeks 6-12, 18, and 26 visits will last approximately one hour and Weeks 14, 22, and 32 visits will last approximately 30 minutes. During these visits, participants will:

- **Female participants only:** Provide a urine sample for a pregnancy test. If the result of the pregnancy test is positive, the participant will not be able to continue in the study. Urine samples will be discarded after testing.**
- Provide a breath sample for a carbon monoxide (CO) assessment. If the session is not completed in-person, CO may be collected using the iCO Smokerlyzer.
- Have weight, blood pressure, and heart rate measured.**

- Review current medications with a member of the research team and provide information on any new medications the participant may have started.
- Have blood sugar measured via a finger prick and a handheld glucose monitor.**
- Fill out questionnaires, including a symptoms evaluation checklist, electronically via REDCap or on paper. These questionnaires will take up to 10 minutes to complete.
- Provide information on medication adherence and return used medication pens.

Weeks 6, 7, 8, 10, 12, 18, and 26 Monitoring Clinic Visits only:

- Attend Target Quit Date (Week 6) and Booster (Weeks 7, 8, 10, 12, 18, and 26) smoking cessation counseling sessions (~30 minutes).

Weeks 7 and 32 Monitoring Clinic Visits only:

- Based on reported smoking behavior, participants may be asked to provide a saliva sample that will be used to examine by-products of nicotine.

Weeks 18 and 32 Monitoring Clinic Visits only:

- Provide an 18.5mL blood sample (less than 4 teaspoons) that will be used to analyze exploratory cardiovascular risk markers.

Weeks 14 and 26 Monitoring Clinic Visits only:

- Schedule the dates and times of the next three 24-hour dietary recalls, which will be completed before the next in-person visit.

** Procedure only completed in session is completed in-person.

7.2.5. Final Check-in

Four weeks (+7 days) after the last study visit, study staff will contact the participant by phone to ask about smoking status (TLFB) and any delayed side effects the participant may have experienced. This call will take up to 15 minutes to complete.

7.2.6. Visit Reminders

For each scheduled study visits participants will receive appointment reminders via phone call, email, or text message (depending on their preference). These reminders will occur 24 – 48 hours prior to study visits and will include important information for the study visit, such as location.

7.2.7. Remote Study Participation

The COVID-19 pandemic has resulted in changes to study procedures due to difficulty completing in-person sessions. In the event that a participant is unable to attend an in-person visit, either due to personal reasons or office closure, procedures will be modified to allow for remote collection of data. The procedure for visit reminders will remain the same. Participants will be contacted via call or text to remind them of the time of their session, as well as to remind them that the session will be conducted by phone. Staff will call participants to complete all measures that can be completed by phone. If collected on-site using session paperwork, these data will be stored in the participants' charts and locked in secure filing cabinets, as is standard procedure. In the event that research staff are off-site, they will utilize Pulse Secure to enable a secure, remote connection to their desktops and the secure server. Data collected remotely will be stored on our secure server, and later transcribed to paper measures and stored in participant charts. Items that are typically dispensed to participants at certain visits may be mailed to the participant, including counseling binders and study materials related to medication use (e.g. medication pen needles, sharps containers etc.). All study sessions can be conducted remotely with the exception of the Intake, Week 1, Week 5, Week 18, and Week 32 visits. We believe this will enable us to continue collection of data in a rigorous way while maintaining the safety of subjects.

7.3. Impact of COVID-19 Quitting Experience Survey

Enrolled participants who completed their final counseling visit (Week 26) as of 3/30/2020 may be contacted to

complete a survey, intended to capture their experience quitting smoking during the COVID-19 pandemic. For participants enrolled after June 8, 2020, this survey will also be administered at intake. Participants will be asked to provide verbal consent for this data collection when contacted, as well as for any future contact needed to clarify any information collected during the survey. Participants will also be asked to provide verbal consent for the recording of the survey. If a participant does not consent to completing the survey or being recorded, the survey will not be administered, and the call will be ended. The call will be recorded using staff recorders (typically used for recording counseling sessions). All recordings will be stored on our secure server, and only staff will have access to those files. Recordings will be used to ensure participant responses were captured exactly when the data is reviewed. Staff will complete the survey via RedCap (i.e. reading off questions and recording answers), and no other personal information will be collected.

The survey will include 24 questions recommended by the NIH for research pertaining to COVID-19, 11 questions related to smoking behavior and the pandemic formulated by staff, and the PHQ-2 and GAD-2 measures for depression and anxiety symptoms (4 questions total). If a participant scores a 3 or higher on either the PHQ-2 or GAD-2 measure, they will be offered resources for coping strategies.

7.4. Description of Study Measures & Procedures

7.4.1. Smoking Cessation Behavioral Counseling

All participants will receive manual-based counseling from either Dr. Ashare or a counselor trained and supervised by the PM or Dr. Ashare. The counseling protocol is based on PHS guidelines for smoking cessation treatment (53), used in Dr. Ashare's prior work (68). The initial 1-hour session (Pre-Quit Session; Week 5) begins with a review of smoking and quitting history, reasons for smoking and quitting, triggers for smoking, obtaining social support for quitting, and self-monitoring of smoking (69). The 2nd session (Target Quit Date; Week 6) will focus on the quit day experiences given that the participant will have been instructed to quit the morning of this session. The benefits of quitting will be emphasized along with evaluating and reinforcing progress with cessation, managing triggers, slip management and recovery, and relapse prevention (70-72). Sessions 3 through 8 (Booster sessions; Weeks 7, 8, 10, 12, 18, and 26) will include evaluating and reinforcing progress with cessation, reviewing trigger management, relapse prevention, problem solving difficulties, and challenges such as slips. The counseling sessions are designed to enhance awareness of the harmful effects of smoking, assist the person in developing skills to quit and avoid relapse. Training and quality assurance measures will be established to ensure optimal delivery of the smoking cessation protocol. Counselor adherence to the treatment protocol will also be facilitated by use of highly structured protocols.

7.4.2. Screening/Covariates

Medical History & Physical Examination: A medical history (self-report) and a physical examination will be conducted at the Intake Visit to review for any contraindications listed previously. The medical history (including height and weight) will be completed by a research staff member. The brief physical examination will be led by a medical professional. Current medical conditions and medications will be documented.

Demographics, Smoking & Alcohol History: Standard questionnaires will be self-administered at the Intake Visit (in-person or remote via REDCap) to collect the following data: demographics (age, gender, marital status, and education), age at smoking initiation, cigarette brand, length of prior abstinence periods, current smoking rate, and number of alcoholic drinks consumed in the past 7 days. The Fagerstrom Test for Nicotine Dependence (FTND) will be administered. This 6-item measure is a standard instrument for assessing the intensity of physical addiction to nicotine. It has good internal consistency ($\alpha = .64$) and high test-retest reliability ($r = .88$) (78). Smoking rate and alcohol use will be assessed throughout the study using a standard timeline follow-back (TLFB) method at each study visit.

Psychiatric History: Current depression, lifetime prevalence of psychosis, bipolar disorder, schizophrenia, hypomanic/manic episodes, substance abuse, and suicide attempts will be determined via self-report during the phone screen and via semi-structured interview using the Mini International Neuropsychiatric Interview (MINI),

the Alcohol Use Disorders Identification Test (AUDIT), the Center for Epidemiological Studies-Depression (CES-D) questionnaire, and the Columbia-Suicide Severity Rating Scale (C-SSRS). The MINI is a 10-15 minute structured interview developed to assess major DSM-V Axis 1 psychiatric diagnoses. This instrument permits both current (past 30 days) and lifetime assessments of psychiatric illness and recent data support its reliability and validity. The MINI will be administered by a trained research staff member at the Intake Visit (in-person or remote via phone or videoconference). The C-SSRS is a two-page structured interview developed by Columbia University, the University of Pennsylvania, and the University of Pittsburgh that assesses current and lifetime suicidal ideation and suicidal behavior in subjects. There will be 100% review of paper MINIs and C-SSRSs by PM, Stephanie Josephson, LCSW, with relevant training, to maintain quality control. The AUDIT is a 10-item measure that was developed by the World Health Organization (WHO) as a simple method of screening for excessive drinking. The Center for Epidemiological Studies-Depression (CES-D) questionnaire is a 20-item measure that asks participants to rate how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely. Response options range from 0 to 3 for each item (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the time, 3 = Most or Almost All the Time). Scores range from 0 to 60, with high scores indicating greater depressive symptoms. Because these assessments may cause an adverse emotional reaction, staff will be trained to deal with such reactions and to provide additional referrals if needed. If necessary, referrals to appropriate psychological services will be provided.

Blood Pressure: At the Intake Visit, participants presenting with elevated blood pressure (i.e., systolic blood pressure greater than 159 and/or diastolic blood pressure greater than 99) will have a second blood pressure reading taken after a ten minute period in which the participants will be instructed to sit comfortably. If, after the second reading, systolic blood pressure remains greater than 159 and/or diastolic remains greater than 99, the participant will be ineligible for the study, unless determined otherwise by the Study PI or Study Physician, upon review.

Blood pressure will be measured at all subsequent in-person visits. If participants present with elevated blood pressure (i.e., systolic blood pressure greater than 159 and/or diastolic blood pressure greater than 99) at any subsequent visit, the staff will follow the same steps listed above. If, after the second reading, systolic blood pressure remains greater than 159 and/or diastolic remains greater than 99, the Study Physician or Study PI will be consulted to discuss whether the participant should continue taking the study medication. Research staff will follow up with the participant accordingly.

Blood Glucose Monitoring: Because liraglutide may lower blood glucose, glucose levels will be measured at each study visit. If the participant is unable to attend a monitoring visit in person, the blood glucose monitoring would be collected during in-person visits at Intake, Week 1, Week 5, Week 18, and Week 32. As recommended by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), blood glucose levels in non-diabetic individuals less than 70 mg/dl may indicate hypoglycemia. The Abbott Precision Xtra Blood Glucose & Ketone Monitoring System will be used to measure blood glucose (https://freestyleserver.com/Payloads/IFU/2017july/ART24315-002_rev-A_WEB.pdf). This device is indicated for home and professional use. As recommended by the manufacturer, the device will be cleaned and disinfected after each use. A trained member of the research staff will obtain a drop of blood (approximately 0.3 microliter) via a finger prick using a lancing device. The device provides a blood glucose reading within 60 seconds. Individuals who have a blood glucose level less than 70 mg/dl will be provided a beverage containing 15 g of carbohydrate (e.g., fruit juice or soft drink) and asked to wait in the laboratory. After 15 minutes, blood glucose will be rechecked to ensure it is greater than 70 mg/dl before allowing the participant to leave. Participants who present with blood glucose less than 70 mg/dl may be withdrawn from the study.

Shipley-2: All participants will complete the Shipley-2, a revision and restandardization of the Shipley Institute of Living Scale (SILS), at the Intake Visit. The Shipley-2 is a self-administered test designed to assess general intellectual functioning in adults and adolescents and to aid in identifying cognitive impairments (140). The scale consists of two subtests, a 40-item vocabulary test and a 25-item test of abstract thinking. The total administration

time is 22 minutes (10 minutes for vocabulary and 12 minutes for abstract thinking). A trained member of the study staff will score the test using Shipley-2 AutoScore Forms.

Withdrawal Symptoms: The Minnesota Nicotine Withdrawal Scale-Revised will measure withdrawal symptoms associated with quitting smoking (79). The scale assesses eight DSM-IV items of nicotine withdrawal including: dysphoria or depressed mood, insomnia, irritability/frustration/anger, anxiety, decreased heart rate, difficulty concentrating, restlessness, and increased appetite/weight gain. Participants will rate the intensity of their symptoms on the following scale: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe and a summary score will be calculated.

Cigarette Craving: The well-validated and reliable 10-item brief Questionnaire of Smoking Urges-Brief (QSU-B) will assess craving for cigarettes (80, 81). The QSU-B contains 2 subscales (anticipation of reward, relief from negative affect).

Mood: The Positive and Negative Affect Schedule (PANAS) will be used to measure positive mood and negative mood (PANAS) (82-84). The two subscales (Positive Affect [PA; 10 items, e.g., enthusiastic, strong] and Negative Affect [NA; 10 items, e.g., distressed, upset]) have 10 items each, are internally consistent in both non-psychiatric and psychiatric samples (α = .79 to 91), and exhibit good convergent and discriminant validity.

Physical Activity: Physical activity will be assessed with the 7-day Physical Activity Recall (PAR) (85-88). The PAR has excellent test-retest reliability (r=0.81) and validity (r = 0.72 heart rate monitor) (89). It is a widely used measure of habitual activity (86, 90, 91). The PAR provides data on frequency, intensity, duration, and kilocalories expended.

Weight Concerns: Weight concerns associated with quitting smoking will be measured with a reliable (alpha =.87) and valid 6–item scale (108, 109). The score is the average of the responses to all items (1= not at all to 10 = very much).

Food Craving Questionnaire & Dutch Eating Behavior Questionnaire: Habitual food cravings will be assessed with the trait version of the Food Craving Questionnaire (FCQ-T). This valid and reliable 39-item measure asks participants to indicate on a 6-point scale the frequency of food craving (never to always) (92, 93). The Dutch Eating Behavior Questionnaire will assess restrained eating (10 items, tendency to restrict food intake), external eating (10 items, tendency to eat in response to food related cues) and emotional eating (13 items, tendency to eat in response to emotions) (94-97). These scales are associated with food craving and response to food cues (98-100). Participants indicate on a Likert-style scale how often each item is applicable to them (1 = never to 5=very often). Disinhibition will be measured with a subscale (16 items) of the Eating Inventory (101-103) that is thought to reflect responsivity to environmental food cues (104), and internal cues (105), and linked to food reinforcement and weight change (106, 107).

Cigarette Ratings and Subjective Effects: The Cigarette Evaluation Scale (CES), developed to assess subjective effects of smoking, is an 11-item Likert-format measure. Questions include items for nausea and dizziness, craving relief, and enjoyment of airway sensations. The Rose Sensory Questionnaire (SQ), a 9-item Likert-format measure, will be used to assess how much participants liked the cigarette smoked and how high in nicotine the cigarettes appeared to be. The questionnaire also includes a diagram of the respiratory tract and asks participants to rate the strength of the cigarette puffs on the participant's tongue, nose, back of mouth and throat, windpipe, and chest. The CES and SQ will be administered at Intake and at Laboratory Visits 1 and 2.

7.4.3. Questionnaires

Concomitant Medication Review: At the Intake Visit, participants will be asked to list all medications (prescription or non-prescription) and/or supplements currently taken and/or recently discontinued (within the past 14 days) as a baseline collection. All information will be collected on a Concomitant Illness/Medication Log that will be maintained in the participant's study chart. Participants who present with a concomitant illness will not be eligible to participate (see Exclusion Criteria above). At every subsequent session, participants will be asked if they have taken any additional medications (prescription or non-prescription), supplements, and/or changed the dosage of any previously reported medications/supplements since their last session. Information collected will include the start date, stop date (if applicable), and indication. The Study Physician and/or Principal Investigator will review any safety concerns and/or study eligibility determinations on a case-by-case basis.

Symptoms Evaluation/Side Effects Checklist: A checklist of symptoms/side effects based on the liraglutide product insert will be administered to participants at all study visits starting at Baseline/Lab Visit 1 (Week 1). The frequency and severity of common side effects of liraglutide will be rated on a 0 (none) to 3 (severe) scale and can be summed to provide an overall side effects index. An open-ended side effects question will also be included. Furthermore, participants will receive written instructions to call the Study Physician should they experience any severe side effects or adverse events between study visits.

7.4.4. Food-Related Tasks

Individualized Food Preferences (Pre-FCQ-S): In preparation for the food cue-induced craving task, participants will rate how appetizing they find pictures of food (e.g., cupcakes, fruits, vegetables) at the Intake Visit. Foods rated least appetizing (n=20) and foods rated most appetizing (n=20) will be selected to create personalized food cue stimuli.

Food Cue-Induced Craving Task: The food cue-induced craving computer task will present (5 sec) 20 pictures of food rated (at Intake) as most appetizing and 20 pictures of food rated (at Intake) least appetizing, and 20 pictures of a water glass. Participants will be instructed to imagine tasting and eating the pictured food for as long as the food is presented. Order of presentation is randomized and the task consists of 60 events separated by an inter-stimuli interval (fixation point) ranging from 2-11 sec (mean 5.5 sec). The food craving assessment is the 3-item "desire" subscale of the reliable and valid state version of the Food Craving Questionnaire (FCQ-S). Total task time: ~10 minutes.

Food Intake (24-Hr Dietary Recalls): Participants will complete three 24-Hour Dietary Recall assessments at four separate time points (prior to Weeks 1, 5, 18, & 32; 12 assessments in total) over the course of the study. During each 24-hour dietary recall, a member of the research team will contact the participant over the telephone during a predetermined time window to discuss their eating and drinking from the day before. The research team staff will use a multi-pass method with an interactive computerized software program, the ASA24® (Automated Self-Administered 24-hour Recall), to determine total kcal/day. The ASA24® was created by investigators at the National Cancer Institute (NCI). If participants are unable to complete a scheduled recall over the telephone, participants may be asked to complete a 24-hour dietary recall with the research staff in-center. Comparable accuracy can be achieved when administered in-person and over the telephone. Food recalls are widely used, reliable, and valid, assessing kcals/day within 10% of actual dietary intake measured under laboratory observation and by doubly labeled water. Each dietary recall assessment will take about 30 minutes. Dietary Recalls can be rescheduled up to 7 days after the corresponding in-center study visit.

7.4.5. Outcomes

Smoking Abstinence (Aim 1) will be assessed at each Monitoring Visit after the Target Quit Date (52) and biochemically verified via a saliva sample at Weeks 1 & 26 post-TQD (Weeks 7 & 32). A reliable and valid timeline follow-back method (110) will be used to assess daily smoking (presence and rate) (65, 67). The primary smoking outcome variable will be 7-day point prevalence abstinence (no smoking, not even a puff, for at least 7 days prior to the assessment) biochemically verified by CO < 5 ppm at 12 weeks post-TQD (Week 18) and EOT (26 weeks post-TQD; Week 32) (64). Carbon monoxide (CO) measures will be made using a Vitalograph Breath CO Analyzer (McNeil International, Inc., Lenexa, KS) or an iCO Smokerlyzer (CoVita, Santa Barbara, CA). The manufacturer will have calibrated this device within the past year. The Vitalograph Breath CO monitor will be used at in-person visits. A new, disposable cardboard mouthpiece will be provided for each participant. The device has a digital screen which reports CO levels in parts per million (ppm). The iCO Smokerlyzer can be shipped to participants and will be used to collect CO remotely. This is a personal carbon monoxide reader that you will connect to your phone and send results to the research team. You will be provided this device by the research team and instructed on how to use it. Participants will be asked to provide a CO breath sample by taking a large breath, holding their breath for two seconds, releasing the breath, then taking another deep breath and holding their breath for 10 seconds, as per the recommendations of the American Thoracic Society. Then, when instructed to do so, participants will exhale as forcefully and as long as they are comfortably capable. The largest value displayed is recorded during all

CO breath samples. We may mail iCO Smokerlyzers (CoVita, Santa Barbara, CA) to participants if they report abstinence from smoking cigarettes at Week 7 or any subsequent session. A participant will use the same iCO Smokerlyzer for the duration of the study. The devices cannot be reused by another participant. During the study visit, we will ask participants to take their CO while on the video call with the study team. They will temporarily leave the Zoom/BlueJeans app and go into their iCO app, and do the CO reading while still on the call with the study staff. Once they have completed their reading, they will be instructed to send the result of the reading to the lab email. CO breath samples will be collected in-person at Intake, Week 1, Week 5, Week 18, and Week 32. CO breath samples at other sessions may be collected remotely if they report abstinence.

Weight Gain (Aim 2) will be measured by digital scale (pounds, ounces) wearing light clothing without shoes prior to each session and at follow-up. Height will be measured at baseline using a mounted stadiometer and BMI calculated as weight (kg)/height (m)2. Pre-cessation weight will be computed as the average of weights at the Intake and Baseline/Lab 1 Visits prior to initiation of study medication. Weight change from baseline to the 26-week follow-up will serve as a primary weight outcome variable (58, 61, 111).

7.5. Tissue Specimens

Urine: A urine sample will be collected at the Intake Visit and each Laboratory Visit (Weeks 1 & 5) for drug and (if applicable) pregnancy tests. Subjects who test positive for study prohibited drugs and/or pregnancy will be not be able to participate in the study. The urine drug screen requires about 30ml of urine and indicates whether the subject has recently taken any exclusionary drugs (cocaine, methamphetamines, PCP, barbiturates, ecstasy (MDMA) or non-prescribed amphetamines, benzodiazepines, methadone, oxycodone, and/or and opiates). In an effort to remain CLIA-compliant, results from urine screenings will not be shared with participants. Participants will be informed that the testing is for research purposes only and that they will be informed of their eligibility status, but not of the specific testing results. In addition, the current protocol does not utilize PennChart and therefore, results of the screening will not be added to participants' electronic medical records. Some OTC and other non-exclusionary medications are known to cause false-positives on urine drug screens. If a participant is believed to have a false-positive result on the urine drug screen, the participant may continue in the study with investigator approval. Urine samples will be disposed of following the conclusion of the study visit.

Blood: One 4mL EDTA tube will be collected at Intake and sent to Quest Diagnostics for a Hemoglobin A1c (HbA1c) Test. Participants will only be considered eligible for the study if this test indicates that they do not have diabetes. One 8.5mL SST tube will be collected at Intake and sent to Quest Diagnostics for a Comprehensive Metabolic Panel (CMP) to assess kidney and liver function. Participants will only be considered eligible for the study if the Study Physician reviews their CMP results and determines it is safe for them to receive the study drug. One 10mL EDTA tube and one 8.5mL SST tube will be collected at each Laboratory Visit (Weeks 1 & 5), Week 18, and Week 32 for exploratory analyses of cardiovascular risk markers. Whole blood will be collected in the EDTA tube and aliquoted into two storage tubes. The SST tube will be centrifuged at 1100 g (3100 RPM) for 10 minutes for serum extraction. Four 0.5mL serum aliquots will be stored in 1.5 mL Eppendorf tubes and stored at -80°C until analysis. These sample will be stored at the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) and analyzed at the Laboratory Biomarkers, Quantitative Pharmacology, Neuroimaging, and Neurobehavioral Characterization Core at the Penn Mental Health AIDS Research Center (PMHARC).

Participants will be given the option to let us store some of their blood for use in future research related to nicotine addiction and/or determining treatments to help people quit smoking. This future research would be reviewed and approved by the University of Pennsylvania Institutional Review Board. Permission to store blood for use in future research is optional and participants will indicate their choice on the informed consent form. Blood samples will be labeled and stored with an identification number only. Sections 10.6.1 and 10.6.2 of this protocol provide information on how study samples and data will be kept private and confidential. Participants may withdraw their permission at any time by contacting study staff and letting us know they no longer want their samples to be stored for use in future research. It is possible participants' samples may be used in future research for commercial

profit. If so, participants will not share in or benefit from this commercial profit. Additionally, individual research results obtained as part of future research will not be shared with participants.

Saliva: If a participant reports not smoking (not even a puff of a cigarette) for at least the 7 days prior to the Week 7 and Week 32 Monitoring Visits, the participant will be asked to provide a 5ml saliva sample used to assess cotinine levels and biochemically verify 7-day point prevalence abstinence. If the participant is unable to attend the in-person session, sample collection kits will be mailed to them if the participant confirms abstinence prior to the Weeks 7 and 32 visits. Saliva samples will be discarded at the end of the study.

7.6. Sample Size Determination

For this analysis we will be estimating summary statistics by group, including means, standard deviations, within-subject correlations, and related confidence intervals. Our sample of 20 participants per group will yield 95% confidence intervals with limits that fall less than 1/2 SD from the mean. For correlation, the 95% CI length will be no larger than 0.94 if r=0, and substantially narrower for r not equal to 0. Because the goal of this study is to demonstrate feasibility and provide preliminary data, we will use these measures to estimate interaction effect sizes to plan future research.

7.7. Statistical Methods

Prior to performing analyses, we will: (a) screen for data-entry errors, (b) check for outliers and missing data, (c) create summary scores, and (d) check distributional assumptions. To minimize missing data we will compensate participants for their time and travel costs to maximize visit and medication adherence and participant retention (e.g., retention rates ~90%) (75, 122). We will assess group differences in attrition and adherence. Per convention, subjects who withdraw or are lost to follow-up during the Cessation Follow-Up phase will be included in the intent-to-treat analysis and coded as smokers.

For Aim 1, we will evaluate whether liraglutide improves abstinence rates (point-prevalence, binary outcome) at the 12 and 26 week post-Target Quit Date follow-up visits. Analyses will be conducted in the context of a longitudinal model with categorical and continuous predictor variables. We will use generalized linear models fitted with random effects using Generalized Estimating Equations. We will specify the logistic model for the binary abstinence outcome, and Gaussian weight gain outcome. Models will include treatment assignment, time point, adherence measures, and covariates related to the outcome in preliminary analyses. Comparisons are all between-subjects. The primary hypothesis will be tested using the z-score corresponding to treatment assignment at 12- and 26-weeks post-TQD, with the primary test of hypotheses 1 at 26-weeks post-TQD.

Analyses for Aim 2 will parallel those described for Aim 1 using body weight (kg; continuous outcome) at the 12 and 26-week post-TQD follow-up visits as the dependent variable. Similar to Aim 1, the primary test of hypothesis 2 is at 26-weeks post-TQD. We will use generalized linear models fitted with random effects using Generalized Estimating Equations. We will specify a Gaussian model for the continuous body weight outcome. Models will include treatment assignment, time point, adherence measures, and covariates related to the outcome in preliminary analyses. Comparisons are all between-subjects. Because we hypothesize that liraglutide will promote smoking cessation by attenuating weight gain, it is possible that treatment effects on attenuating post-cessation weight gain will be mitigated by individuals who relapse (and thus do not gain weight). Therefore, weight gain will be assessed in the context of abstinence and relapse. Although we are not powered to test the interaction of treatment by smoking status, we will explore this possibility to inform future research.

For exploratory outcomes, we will evaluate the effects of liraglutide on food intake and the reinforcing value of food. We will compare food intake, measured via total calories consumed reported on the 24-hr dietary recalls, and the reinforcing value of food (i.e., maximum amount of responding for food vs. money) following 5-weeks of treatment with liraglutide or placebo. Specifically, we will use repeated measures regression models and include a term for time (baseline [Week 1] vs. Week 5) in each model as well as a between-subject factor of medication

group (liraglutide vs. placebo). Models will include medication group, time point, adherence measures, and covariates related to the outcome in preliminary analyses.

Interim Analysis
Because this is a pilot study, we have no plans to conduct an interim analysis.

Evaluability of Subjects
All eligible smokers who complete the initial Intake Visit will be randomized. Consistent with intent-to-treat analyses, we will measure smoking cessation and weight gain in the entire sample at the 4-week post-TQD follow-up (Week 10). As is the convention in smoking cessation trials, smokers who are lost to follow-up will be included in the analysis and counted as smokers (65, 66, 127). We will examine the characteristics of those subjects who drop out to identify any associations between dropout and baseline measures. These analyses will be descriptive, as we expect few dropouts. Items missing at random will be imputed prior to calculating final scores using conditional means, estimated with a version of Buck's method (128). The analyses will also be repeated using only complete observations to assure that parameter estimates are not impacted by imputation.

Sensitivity Analysis
Given the substantial changes required to study procedures due to the COVID-19 pandemic, we will conduct a sensitivity analysis to evaluate the impact of the transition to remote visits on study results. We will utilize a 'clustering' approach and assess the impact of clustering by analyzing outcomes with and without taking clustering into account: comparing the analysis that ignores clustering (i.e. assumes that the data are independent) to a method that will account for clustering (141). To account for clustering, we will include a variable to compare subjects who completed the trial pre-COVID (all in-person) to those who completed the trial post-COVID (mostly remote visits with some in-person tasks).

8. RISKS / BENEFITS

8.1. Potential Study Risks
A detailed description of the study will be given to all participants, which will include the risks of participation, actions taken to mitigate potential loss of confidentiality, and the knowledge that their freedom to refuse participation or withdraw from the study will not affect the availability of treatment at the University of Pennsylvania. Informed consent procedures will comply with current standards of the IRB at the University of Pennsylvania. Subjects can choose, as an alternative, not to enroll in this study. Adverse reactions will be assessed and reported as required by Federal law and the regulations of the University.

Study Medication (liraglutide):
In several clinical trials that lasted at least one year, the following side effects were reported in greater than 5% of people taking liraglutide and more frequently than in people taking a placebo:

- Nausea
- Diarrhea
- Vomiting
- Indigestion
- Dizziness
- Low blood sugar (Hypoglycemia)
- Constipation
- Abdominal pain
- Headache
- Fatigue
- Increased lipase

The clinical significance of elevations in lipase or amylase with Saxenda® is unknown in the absence of other signs and symptoms of pancreatitis.

Adverse reactions reported in greater than or equal to 2% of people taking liraglutide and more frequently than in people taking a placebo included:

- Bloating
- Belching
- Flatulence
- Dry mouth
- Insomnia
- Anxiety
- Gastroesophageal reflux disease (GERD)
- Injection site erythema (redness)
- Injection site reaction
- Asthenia (weakness)
- Gastroenteritis (stomach flu)
- Urinary tract infection

If participants experience any severe side effects or related medical issues during their participation in the study, it is important that they contact research staff and/or the Study Physician (listed on page one) at the telephone number provided as soon as possible. The Study Physician's emergency contact information is also on the medication package that they will receive from us.

Thyroid C-Cell Tumors: Liraglutide causes both cancerous and non-cancerous thyroid C-cell tumors in mice and rats. The relevance of this finding to humans has not been determined. Individuals with a personal or family history of thyroid tumors are not eligible for this study. Participants should tell their primary care provider (PCP) and the study staff if they get a lump or swelling in the neck, hoarseness, trouble swallowing, or shortness of breath as these may be symptoms of thyroid cancer.

Inflammation of the Pancreas: Inflammation of the pancreas (pancreatitis) has been observed in some patients taking liraglutide. Participants should contact their PCP and the study staff if they experience severe pain in their stomach area (abdomen) that will not go away, with or without vomiting. If pancreatitis is suspected, the participant will be instructed to stop taking liraglutide and will be withdrawn from the study.

Gallbladder Problems: Gallbladder problems, including gallstones, have been reported in some patients taking liraglutide. Participant should contact their PCP and study staff if they experience pain in their upper stomach (abdomen), fever, yellowing of skin or eyes (jaundice), or clay-colored stools. If cholelithiasis (gallstones) or cholecystitis (gallbladder inflammation) are suspected, the participant will be instructed to stop taking liraglutide and will be withdrawn from the study.

Increased Heart Rate: Liraglutide may increase heart rate while at rest. During this study, participants' heart rate will be measured regularly to monitor for any changes. Participants should contact their PCP and study staff if they feel their heart racing or pounding in their chest and it lasts for several minutes.

Kidney Problems: Liraglutide may cause nausea, vomiting, or diarrhea leading to loss of fluids (dehydration). Dehydration may cause kidney failure which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce the chance of dehydration. Participants should contact their PCP and study staff right away if they have nausea, vomiting, or diarrhea that does not go away, or if they cannot drink liquids by mouth.

Depression or Thoughts of Suicide: Individuals who are at risk for suicide attempts or those with active suicidal thoughts should not take liraglutide. This is why study staff will ask participants about these issues during the Intake Visit. Participants' mood will be monitored throughout this study. Participants should pay attention to any mental changes, especially sudden changes, in their mood, behaviors, thoughts, or feelings. Participants should contact their PCP and study staff right away if they have any mental changes that are new, worse, or worry them. Participants who endorse current suicidal thoughts or behaviors will be instructed to stop taking liraglutide and will be withdrawn from treatment.

Potential Drug Interactions: Liraglutide delays stomach emptying and can affect medicines that need to pass through the stomach quickly. Taking liraglutide may impact the absorption of some oral medications and how

they work. Participants should contact their PCP and study staff if they feel delays in stomach emptying, such as feeling uncomfortably full after little food is eaten.

Unforeseen Risks: People may have allergic reactions to medications. A severe allergic reaction could be life-threatening. Examples of an allergic reaction include rash, difficulty breathing, wheezing, sudden drop in blood pressure, fast pulse, sweating, and swelling around the mouth, throat, or eyes. There may be other risks associated with liraglutide that have not been identified. If additional risks are identified during the study, the study team will inform participants. If an allergic reaction or hypersensitivity reaction occurs, the participant will be instructed to stop taking liraglutide and seek medical attention. The participant will be withdrawn from treatment.

Reproductive Risks (Females Only): The use of liraglutide may pose risks to pregnancy and an unborn child. Therefore, participants should not become pregnant while they are in the study. If a participant are able to become pregnant, she will be required to follow a study-approved method of birth control while participating in the study. Adequate birth control in this study is the use of double barrier methods (condom with spermicide or diaphragm with spermicide), stable hormonal contraception (such as oral contraceptive pills, Depo-Provera injection or the contraceptive patch), intrauterine device (IUD), abstinence, or tubal ligation.

Liraglutide may also have unknown risks for breast-fed babies. Therefore, participants should not breastfeed while you in the study.
Although pregnancy testing will be performed during the study, it is possible that the results could be wrong. If a participant does become pregnant while in this study, she will be asked to immediately notify the study team, discontinue the study drug/placebo, and consult an obstetrician or maternal-fetal specialist. If a participant becomes pregnant, we will break the study blind and find out if the participant was taking the study drug or placebo. The Study Physician or Nurse Practitioner will remain in contact with the participant to learn the outcome of the pregnancy. If the participant was taking the study drug, the Study Physician or Nurse Practitioner will confirm that she is consulting with an obstetrician or a maternal-fetal specialist, record any complications, and obtain information regarding the overall health of the participant and the baby. The Study Physician will share this information with the University of Pennsylvania Institutional Review Board and with Novo Nordisk, the company that manufactures liraglutide.

Subcutaneous Injection: Risks of subcutaneous injection of the study medication or placebo include pain or discomfort, bruising at the puncture site, swelling, feeling faint or lightheaded, and (rarely) infection.

Withdrawal: Many people who smoke cigarettes have symptoms of withdrawal when they stop smoking. These symptoms can occur almost immediately and last for about 7-10 days. These symptoms can include: sadness and mood changes, insomnia, anxiety, constipation, decreased heart rate, muscle pain, irritability, craving for nicotine, headaches, anger, difficulty concentrating, restlessness and nervousness, and appetite change and weight gain. These symptoms are usually low risk. The study staff know how to identify these symptoms and inform you about them. Although nicotine replacement therapy may help reduce withdrawal symptoms, we ask that you do not use any nicotine-containing products (other than your cigarettes) for the duration of the study.

Psychological Distress: Participants may experience emotional distress during assessments from discussing feelings and attitudes about smoking and/or from learning about the risks of smoking. This happens rarely and, in almost all cases, does not last long and is of low intensity. The research staff that work with participants know how to help if participants have any concerns.

Blood Draws: Blood draws may result in bruising and/or slight bleeding at the needle site or may cause you to feel faint. All of these side effects are rare. Blood will be drawn by a trained professional to reduce the risk of these discomforts.

Email Communications: Throughout this study participants may get appointment reminders via email or choose to ask questions related to the study via email. Email is not a secure method of communication. Email messages travel across the Internet passing through multiple computers before reaching their final destination. It is not possible to know whether an email you send will be viewed along the way. Additionally, if sent messages are not deleted, an email provider may have a folder of everything that is sent. If someone gets access to an email account (for example, a family member), they could see old messages. There are many other ways in which emails are not secure—these are only selected examples. For these reasons we ask that participants only use email communication for routine matters and never for personal or confidential messages or questions. If participants have questions or concerns that are personal in nature, we suggest participants contact the study staff via phone.

Loss of Confidentiality: As this study involves the use of participants' identifiable, personal information, there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to lessen the possibility of this happening (see Section 10. Data Management).

8.2. Potential Study Benefits

It is not known if the study medication (liraglutide) will cause any change in smoking behavior. Participants who enroll in this study may benefit from the knowledge that they are contributing to the advancement of treatments to help people quit smoking. All participants will receive smoking cessation counseling which may help them make a successful quit attempt.

8.3. Risk/Benefit Assessment

There is minimal risk for serious adverse events by enrolling in this research study. The treatments and procedures used in this study have been shown to be relatively safe. Research staff will monitor participants closely throughout the study. Thus, the risk to benefit ratio for this project is perceived to be low and justifies its implementation.

9. Safety and Adverse Events

9.1. Definitions

Adverse Event (AE) means any undesired medical event occurring (including an abnormal laboratory finding, symptom or disease temporarily associated with the use of a product) to a subject in a clinical trial, whether or not related to the Study Drug.

Serious Adverse Event (SAE) means a serious Adverse Event that at any dose

1. Results in death;
2. Is life threatening;
3. Requires inpatient hospitalization or results in prolongation of existing hospitalization;
4. Results in persistent or significant disability/incapacity;
5. Is a congenital anomaly/birth defect; or
6. Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered a "Serious Adverse Event" when, based upon appropriate medical judgment, such event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in this definition.

Serious and Unexpected Suspected Adverse Reaction (SUSAR) means a Serious Adverse Event which is unexpected and regarded as possibly or probably related to the study drug by the Sponsor-Investigator.

AE Reporting Period

The study period during which adverse events must be reported is the period from the initiation of any study procedures (signing informed consent) to the end of the study treatment follow-up. For this study, the study

treatment follow-up is defined as 4 weeks following the last administration of study medication. A compilation of any Adverse Events will be provided in the annual and final progress reports to Novo Nordisk.

Pre-existing Condition
A pre-existing condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Hospitalization, Prolonged Hospitalization, or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Pregnancy
Study subjects will be instructed to notify the PI (Dr. Ashare) immediately if they become pregnant. Dr. Ashare will report any pregnancies occurring during the trial to Novo Nordisk using the same guidelines as described for AEs. Pregnancy complications will be recorded as AEs. If the infant has a congenital anomaly/birth defect this must be reported and followed up as a Serious Adverse Event.

Precautions/Over-dosage
Effects of overdoses have included severe nausea and severe vomiting. In the event of over-dosage, appropriate supportive treatment will be initiated according to the patient's clinical signs and symptoms.

9.2. Collection and Recording of Adverse Events

9.2.1. AE Collection Methods

All AEs and SAEs occurring during the study period will be captured through the measures described below:

1. Participants will complete a symptoms evaluation/side effects checklist (SEC) at all study visits from the first study-related activity (signing of informed consent). The SEC will assess the severity of side effects (defined as AEs) that may be drug related and experienced by participants in the study. Items will be rated by participants utilizing the following severity scale: 0 (None=No Concerns), 1 (Mild=Side effect or event does not interfere with usual daily activities), 2 (Moderate=Side effect does interfere with some activities), and 3 (Severe=No normal activities are possible).

2. Participants will complete an open-ended SEC form at all in-person study visits from the first study-related activity (signing of informed consent). The open-ended SEC form will assess any symptom, medical issue, or concern that may be related to a subject's participation not included on the SEC. The reporting period for each assessment will inquire about any symptom(s)/medical concern(s) experienced since the last in-person visit. If a participant reports a symptom(s) or medical concern(s), they will be asked to rate the severity of the event utilizing the following severity scale: 0 (None=No Concerns), 1 (Mild=Issue does not interfere with usual daily activities), 2 (Moderate=Issue does interfere with some activities), and 3 (Severe=No normal activities are possible). Follow-up information surrounding the report will be collected

as necessary.

3. Once enrolled, participants will be instructed to inform (spontaneous assessment) the study staff of any notable symptom, medical issue(s), or concern throughout the study. Participants will also receive an emergency medical card with the Study Physician's contact information should the medical issue or concern require immediate attention.

4. The current version of US Prescribing Information (i.e., label) or any updates made during the study will be used in the assessment of expectedness of an adverse event.

9.2.2. AE/SAE Documentation and Internal Reporting Procedures

AE/SAE Documentation: As noted above in section 9.2.1, research staff are trained to collect follow-up information about any severe or moderate AEs reported on the SEC Form, any medical event(s) reported on the Open-Ended AE Form, or any notable spontaneously reported medical event or concern. At a minimum, follow-up information will include AE/SAE onset/resolution, description of event/course, severity, action taken, outcome, and possible relation to liraglutide (if applicable).

Information surrounding AEs and SAEs will be initially recorded on the appropriate source document such as the SEC Form, Open-Ended AE Form, an "AE Note" or SAE Form, and/or any document in which the AE/SAE information was originally recorded. All applicable AEs and SAEs will then be documented on a cumulative AE and SAE log maintained within the study database.

Completed documentation of applicable AEs will include the following information:

- Protocol Title and IRB#
- Subject Identifier
- Event Title
- Date Site Notified
- Event Start Date
- Event Stop Date
- Description of Event/Course (including sequelae)
- Severity:
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI and/or Study Physician):
    - Unrelated = Definitely not related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Expectedness per protocol and/or consent
    - Expected
    - Unexpected
- Action(s) taken (if appropriate)
- Outcome (if appropriate)

Documentation of SAEs will include the following information on a standardized SAE Form:

- Protocol Title and IRB#
- Subject Identifier
- Demographic data

- Liraglutide/placebo Lot number, expiration date, and other descriptive information (if appropriate)
- Date Site Notified
- Date of SAE onset
- Date of SAE resolution, if available
- Course/Description of Event (including sequelae)
- Action(s) Taken
- Outcome
- Follow-up plan
- Severity of the event
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI and/or Study Physician):
    - Unrelated = Definitely not related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Expectedness per protocol and/or consent
    - Expected
    - Unexpected
- Clinical assessment of subject conducted at time of SAE (if appropriate)
- Results of any laboratory tests and/or diagnostic procedures (if appropriate)
- Autopsy findings (if appropriate)
- Concomitant medications and therapies (excluding treatment of event)
- Relevant Medical History (if appropriate)

Internal Reporting Procedures: All relevant follow-up information outlined above (see AE/SAE documentation) concerning applicable AEs, including all information regarding the occurrence of concurrent smoking and liraglutide (if applicable) and previously reported event(s) and/or side effects, will be reported to the Principal Investigator, Study Nurse Practitioner, and/or Study Physician to determine a course of action (e.g. continue to monitor, reduce medication dose, stop medication), relatedness (causality) to the study, and expectedness (if not already established). This consult will be documented via email. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not (or unlikely) to be the cause.

SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome unless it has been determined that the study treatment or participation is not the cause. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately per this protocol.

9.3. Reporting of Adverse Events and Unanticipated Problems

AE reporting requirements are detailed in the following sub-sections:

9.3.1. Investigator Reporting: Notifying Novo Nordisk

The study Sponsor-Investigator is required to report certain study events in an expedited fashion to Novo Nordisk, the producer of the medication utilized in this study. The following describes specific events and the corresponding reporting requirements:

- Within 7 calendar days

Any adverse event that is:
- associated with the use of the study drug (probably or definitely related),
- unexpected,
- fatal or life-threatening

- Within 15 calendar days

Any adverse event that is:
- associated with the use of the study drug (probably or definitely related),
- unexpected and
- serious, but not fatal or life-threatening

-or-

- a previous AE that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Any finding from tests in laboratory animals or in vitro testing that:
- suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Findings from other studies that:
- suggest a significant risk for human subjects exposed to the study drug.

Increased rate of occurrence of serious suspected adverse reactions:
- any clinically significant increase in the rate of a serious suspected adverse reaction over that listed in this protocol or the drug label.

All serious drug-related adverse events will be reported to the study drug supplier within 24 hours of learning of the event. The Principal Investigator shall make available to the study drug supplier promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by the study drug supplier.

Novo Nordisk (Study Drug Supplier): Reports of all serious drug-related adverse events shall be made to the study drug supplier (Novo Nordisk) at the same time they are reported to regulatory authorities or within 15 days from the investigator becoming aware of such AEs, whichever comes first.

If Serious Adverse Events, pregnancies and/or other events are reported to Novo Nordisk, the Sponsor-Investigator shall provide randomization lists with actual treatment to Novo Nordisk at the end of the study.

9.3.2. Investigator Reporting: Notifying the Penn IRB and the ACC CTSMRC

Notifying the Penn Institutional Review Board (IRB)

A reportable event is an adverse event or incident that has the potential to be classified by the IRB as an unanticipated problem posing risks to participants or others. In general, an incident is determined to be a reportable event when it is both

1. unexpected in terms of nature or severity or frequency
2. probably or definitely related to participation in the research.

If an adverse event that meets these criteria, the IRB requires investigators to submit within 10 business days of discovery. However, if the event involved a death and indicates that participants or others are at risk of increased harm, investigators should report within 3 days. If the investigator does not have enough information to complete the Reportable Event form within this timeframe, a Reportable Event Form will be submitted and indicate that a follow up report will be provided once additional information has been obtained.

Reportable Events include:

(1) ADVERSE MEDICAL EVENTS WHICH ARE BOTH RELATED AND UNEXPECTED:

- An event is considered "related to the research procedures" if the cause of the event is deemed probably or definitely related to the investigational product or a procedure that was performed for the purposes of the research.
- A "suspected adverse reaction" could be considered a reportable event when there is reasonable possibility that the drug/investigational product caused the adverse event. For these reporting purposes, reasonable possibility means there is evidence to suggest a causal relationship between the drug/investigational product and the event
- If the Sponsor determination notes a causal relationship between the event and the investigational drug/product without required revisions to the consent form or other study documents and/or the report indicates that the event does not alter the risk profile of the investigational drug/product, the event should not be classified as reportable
- An event is "unexpected" if it is not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, the investigator's brochure/package insert, or, the current IRB – approved informed consent document. An event can also be considered unexpected if is not listed at the specificity or severity that has previously been observed and described in the protocol-related documents.
- "Unexpected" also refers to events that are mentioned in the investigator's brochure/package insert as occurring with a class of drugs or as anticipated, but, are not mentioned as to have been

(2) UNANTICIPATED ADVERSE MEDICAL DEVICE REACTION:

- Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

(3) NON-MEDICAL EVENTS - THE IRB ALSO REQUIRES PROMPT REPORTING OF THE FOLLOWING EVENTS:

- Withdrawal from marketing for safety concerns of a drug, device, or biologic used in a research protocol.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
- Premature completion of a study for any reason

All adverse events that are not considered reportable events as defined above will be submitted to the IRB at the time of Continuing Review.

<u>Notifying the Abramson Cancer Center Clinical Trials Scientific Review and Monitoring Committee (ACC CTSRMC)</u>
All adverse events meeting the following reporting requirements will be entered into the Penn Clinical Trials Management System (PennCTMS) AE/SAE form.
On-Site subjects

1. All grade 3 or higher events regardless of attribution or expectedness within 10 business days of knowledge.
2. All unexpected deaths within two business day of knowledge.
3. All others deaths within 30 days of knowledge. Deaths of subjects greater than 90 days from the last study

treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

Protocol Exceptions
An exception is a one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and ACC approval is required.

Protocol Deviations
A deviation is a one time, unintentional action or process that departs from the IRB and CTSRMC approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints), or compromises the safety and welfare of the subjects, the major deviation must be reported to the ACC and the IRB within 10 business days of discovery.

Minor deviations that do not meet the definition above will be explained in a memo to file or recorded on a deviation log and will contain documentation of the PI's assessment of the impact of the deviation on safety and study outcomes. Minor deviations will be reported to the IRB and ACC at the time of Continuing Review.

9.4. Premature Termination of the Study
The study will be stopped if any of the following occur:

- There is clear evidence of harm or harmful side-effects of the treatment.
- There is no likelihood of demonstrating treatment benefit.

9.5. Medical Monitoring
It is the responsibility of the Principal Investigator and Study Physician to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of AEs/SAEs as noted above, as well as adherence to the study data and safety monitoring plan outlined in Sections 9 and 11.

10. DATA MANAGEMENT
The CIRNA Data Management Team has developed a data management system (DMS) that will facilitate the operational facets of this study, including collection, validation and storage of participant data, tracking recruitment call attempts, participant study milestones, and accrual goals, and exporting data for use in statistical analysis and data sharing. The DMS integrates Microsoft Access, REDCap and AutoData Scannable Office.

REDCap (Research Electronic Data Capture) is the primary software platform for collecting and storing questionnaire data. REDCap is a web-based application developed by Vanderbilt University to capture data for clinical research. It is HIPAA-compliant, and highly secure. REDCap ensures data integrity through range and validity checks during the data entry process. In addition to REDCap, some data will be collected using scannable forms created in AutoData Scannable Office. Scannable Office uses Microsoft Word to create forms that are mapped to a MS Access database and processed with an imaging scanner. During the scanning process, response data is captured and written directly into the database.

Microsoft Access is a relational database product and the primary software platform for project management. The MS Access databases contain VBA programming to automate report generation (e.g., accrual, enrollment, medication side effects, participant compliance, and recruitment sources), calculate study milestone dates, calculate study compensation, perform range/validity checks as users enter data, generate custom error messages to control user input, and populate information displayed on participant study materials.

10.1. Data Management System Development
The CIRNA Data Manager will work closely with the trial investigators to develop an understanding of the data collection, storage, and quality assessment needs for the trial. This includes the design and development of the trial data collection forms and any additional administrative CRFs, to ensure that standardized, uniform data

collection and data management procedures are implemented and sustained throughout the trial. The data collection forms will serve as templates for designing the data entry screens. The Data Manager will work closely with trial investigators and senior personnel to design, develop, and test an appropriate database structure to support the requirements of the DMS and to promote data security and integrity. Electronic audit trails of changes to REDCap database contents are incorporated into the design and will capture and record those changes automatically. In addition to the trial database where actual results will be maintained, a development database will be created. The development database is a working environment that facilitates the development, testing, troubleshooting, enhancement, and training for the DMS without adversely affecting the integrity of the collected project data.

Prior to deployment and use by the research staff, the database and DMS will be subjected to extensive functional testing. This testing is conducted according to a written test plan and is intended to verify the proper functioning of all components of the DMS. Any components that do not function as they were intended will be identified and evaluated by the development team to determine appropriate corrective action. Testing will also include an evaluation by user representatives for adherence to the requirements established by the intended users for the DMS. Successful completion of these user acceptance tests will mark the end of development and predicate the deployment of the DMS for use in storing and managing active trial data. Any modifications made to the DMS will be conducted in accordance with change control procedures.

10.2. Data Security

Data collected in MS Access and REDCap databases will be stored on a secure server administered by the Penn Medicine Academic Computing Services (PMACS) organization and will be restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments will also be employed so a user has access only to the functions necessary to complete applicable operations appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies. The Data Manager will maintain the database in an appropriate manner for the retention period required by regulation. Database administration includes user account maintenance, database security, performance monitoring, and database change management. Daily backups are performed to protect data against accidental destruction or corruption.

10.3. Data Processing

The data entry screens will resemble the data collection forms as closely as possible to allow visual referencing during data entry. This data entry module will be configured for single data entry. The majority of participant data will be self-report and participants will enter data into REDCap using tablets during in-person visits. Some data will be collected by research staff, recorded on study-specific CRFs, and scanned in or entered directly into REDCap or MS Access. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and/or skip pattern enforcement. Following initial eligibility screening, research staff will perform subject registration.

10.4. Data Quality Assurance

Data quality modules will be developed by the Data Manager to identify data items that may have been collected incorrectly or entered into the database inaccurately. The modules will run automatically to inspect all newly entered or modified data. The research staff will review the results of the data validation and take any required corrective action for invalid data. Corrections identified for individual data items will be managed by the research staff. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

Monitoring of trial progress will be accomplished, in part, through the use of standard reports. The Data Manager will program a set of standard enrollment, tracking, quality review, and safety monitoring reports. Data audits will occur after the first few participants are enrolled and periodically during the trial to detect errors in data entry. Eligible participants will have 100% of their source document information compared with the data entered in the database. Any errors will be investigated, resolved, and a plan will be implemented to prevent further errors should concerning patterns emerge.

10.5. Subject and Specimen Tracking

The Data Manager will develop a module to assist research staff in recruitment and retention tracking for trial participants. This module will accept and store contact information for potential participants and will include data items to indicate the completion status of significant events. The tracking module will include information about contact and visit schedules to assist in preparing communications to potential subjects and trial participants concerning scheduled events. The module will also allow for incentive-related inventory management. When obtaining blood and saliva specimens, the research staff will complete a specimen registration CRF and scan/enter the data into the DMS. A unique specimen identifier will be assigned and recorded on the CRF. Labeled specimens and applicable information will be transferred to the lab as required for analysis.

10.6. Data Handling and Record Keeping

10.6.1. Confidentiality

Information about study participants 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:

- What protected health information (PHI) will be 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 a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should 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.

Confidentially of study data will be maintained in the following manner:

- Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- Prior to access to any study-related information, personnel will be required to review and sign statements agreeing to protect the security and confidentiality of identifiable information.
- Whenever feasible, identifiers will be removed from study-related information.
- Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
- Audio recordings will be reviewed by the Principal Investigator and senior personnel for training purposes and then deleted to eliminate audible identification of subjects.
- Remote study sessions will be conducted via phone or via BlueJeans, which is a HIPAA-compliant platform with security features including a room lock to ensure that communications within the platform remain private.

Since self-report and biological data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the Data Management System has set up several safeguards to prevent unauthorized access to participant data. In the subject map table, an automatically generated index number is assigned to a subject's study identification number. A linked subject identification table is created to store subject name, address, and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information are maintained in separate locations. Using this method, no identifying subject information is directly linked to bio-samples or results. Any publication of data will not identify participants by name or with an identifier that could be used to reveal identity.

All biological samples will be labeled with study ID only. All participant data that can be linked to the study ID will be stored in the secure Data Management System, which has limited, password-required access. The aforementioned precautions and procedures will be applied to protecting subject privacy and the protected health information detailed in Section 10.6.2 below.

10.6.2. Subject Privacy & Protected Health Information

The following protected health information (PHI) may be collected as part of this study:

- Name, address, telephone number, email address
- Date of birth
- Social Security Number (W-9 form)
- Medical Record Number
- Some personal information that may be considered sensitive, such as medical history, psychological history, alcohol use history, etc.
- Results from physical examinations, questionnaires, or procedures as outlined in this protocol

Potential participants will be contacted over the phone after responding to recruitment efforts or having agreed to be contacted for future studies. Only individuals who have responded to recruitment efforts or who have agreed to be contacted regarding research studies at our Center will be contacted. If an individual cannot be reached immediately, staff members will identify themselves only as calling from the University of Pennsylvania; no mention will be made of the inquiry regarding study participation. Participants will undergo an initial telephone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they be asked to attend an in-person Intake Visit to confirm eligibility. All data collected over the phone, BlueJeans, and during in-person visits will be collected by research staff that have completed the CITI-Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Once enrolled, information will never be recorded with identifiers other than study ID. A separate list of names with ID numbers will be accessible only by authorized personnel. All records will be kept in locked filing cabinets to maintain confidentiality. All analyses will be conducted on de-identified data.

Data will be accessible only to the Study Investigators, Study Physician, study staff, applicable Center staff, UPenn IRB, Office of Clinical Research, authorized UPENN staff (e.g. accounting and billing matters, oversight and monitoring, provide treatment, etc.), Abramson Cancer Center, the National Institutes of Health, and the FDA.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify a subject directly. At most, the website will include a summary of the results. Participants may search this website at any time.

11. DATA AND SAFETY MONITORING

11.1. Research Roles

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal

Investigator, Study Physician, research staff, and the IRB. The research staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms (CRFs), ensuring all fields are completed appropriately, and all error corrections are done according to GCPs. Any inconsistencies/deviations will be documented and addressed as appropriate. The research staff will perform regular chart reviews to verify data integrity. The Project Manager (or senior personnel) and Principal Investigator will maintain the study regulatory binder/essential documents per GCP. The Study Physician/Nurse Practitioner will be available to review medical issues related to participation for each participant on an ongoing basis as outlined in this protocol. Research staff will meet and communicate on a regular basis to reconcile data queries and safety concerns. The IRB will review the trial on an on-going basis per institutional and federal regulations until the study is formally closed-out.

11.2. Staff Training

Staff training will consist of an initial explanation and review of the protocol, informed consent form, CRFs and laboratory tasks, sample collection protocols, data management system, adverse event collection and reporting, and all study-specific SOPs. In addition, during a standardized training period, the duties of each staff member will be clearly outlined and all applicable regulations will be reviewed. The Principal Investigator, Dr. Rebecca Ashare, will oversee the smoking cessation counseling training. Training interactions will be documented in a training log, which will be maintained within the electronic regulatory binder. Senior personnel will supervise junior staff and provide re-training as needed.

All personnel working on this project will complete required training in the protection of human subjects and the protection of personal identifiable information (i.e. HIPAA) and Good Clinical Practices before interacting with study data or research participants. All human subject and privacy protections certifications will be maintained in the electronic regulatory binder.

11.3. Monitoring Activities

11.3.1. AE/SAE Monitoring

Monitoring and management of AEs/SAEs will be conducted in real-time by the Principal Investigator, Study Physician, Nurse Practitioner, and the research team at regular time points as per the methods and procedures detailed in Section 9: Safety and Adverse Events.

11.3.2. Initial Assessment (Intake) Monitoring

The study staff will conduct a manual review of source documents for all subjects determined to be eligible at pre-screening prior to the Intake Visit. Eligibility data will be reviewed in real-time at the Intake Visit by the research staff. Once all eligibility data has been collected, the Study Physician will review participants' eligibility and medical information to determine approval for the distribution of study medication. This determination will be documented via signature on the eligibility checklist or via email and kept in participants' study charts. Once distribution of study medication is approved, the Study Physician or Study Nurse Practitioner will sign a study medication prescription blank that will be sent to Investigational Drug Services.

11.3.3. Protocol Monitoring

Protocol monitoring includes a survey of those activities that are associated with protocol adherence such as identifying, reporting, and rectifying protocols deviations, reviewing for violations of inclusion/exclusion criteria, and ensuring the adherence to study-specific SOPs, GCP, and other federal and institutional regulations.
Protocol monitoring will be performed on an ongoing basis through the following methods:

1. Checklists will be utilized at all time points to ensure all data is collected per protocol and procedures are followed as appropriate.
2. A Final Eligibility Checklist will be completed after the Intake Visit for all participants who enroll (i.e. sign consent) in the study. The Final Eligibility Checklist will serve as final confirmation of eligibility status prior to seeking approval for distribution of study medication from the Study Physician.

3. An internal chart review procedure will be completed for ~25% of randomly selected eligible subjects. The chart review procedure is a thorough review of all source documentation to ensure the integrity of the data, all study paperwork is present, all fields are completed per GCP, and all study-specific SOPs have been followed appropriately.

11.3.4. Database Auditing

As outlined in Section 10: Data Management, the study DMS will be equipped with internal validation checks to ensure data is entered within reasonable ranges. Error messages will be displayed in real-time if data appears inaccurate. Staff will have to respond to these error messages before data can be saved. In addition, The Project Manager/Study Coordinator (or senior personnel) will perform regular milestone quality assurance checks.

11.3.5. Data Security

As outlined in Section 10: Data Management, study data will be secured through controlled user access and accessible to authorized personnel only. Source documents will be secured in locked filing cabinets.

11.4. Frequency of Data and Safety Monitoring

Data will be reviewed internally on a regular basis. Specifically:

1. At data capture, the research staff will review data for completeness and integrity.
2. At data entry, the DMS will include multiple internal validity checks which will prompt the staff if an entry was made that is out of range or in an unacceptable format.
3. Eligibility data will be reviewed in real-time at the Intake Visit. In addition, the Principal Investigator/Project Manager (or senior personnel) will review and verify that all data have been collected and, when applicable, meets the eligibility criteria on a "Final Eligibility Checklist."
4. Between the Intake Visit and distribution of study medication (Lab Visit 1), the Study Physician will receive confirmation from the study staff that a participant has met all the eligibility criteria via email. Any additional eligibility queries will be addressed at this time as well. No study medication will be distributed without documented approval of the Study Physician via email.
5. On a regular basis, the project staff will review data through an internal chart review procedure supported by the DMS. A random subset of eligible participants (~25%) will be reviewed.
6. All CRFs for eligible subjects are 100% source-data verified through an internal data management system (Data Entry/Quality Assurance) on an ongoing basis.
7. The study statistician will review data prior to analysis to ensure integrity and validity.

11.5. Auditing and Inspecting

The Principal Investigator will permit study-related monitoring, audits, and inspections by the IRB, the Sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The Principal Investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11.6. Liability and Subject Insurance

Throughout a participant's participation in the study and following a participant's participation in study, the Principal Investigator, study team, and the University of Pennsylvania will provide adequate medical care to the study participant for any study-related adverse events, including clinically significant laboratory values related to the study. We may bill a participant's insurance company or other third parties, if appropriate, for the costs of the care, but this medical care for study participants will be provided regardless of their insurance status.

Dr. Ashare (PI) and the study team will be responsible for the conduct of the study. The Trustees of the University of Pennsylvania shall be responsible for any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from the conduct of the study and to the extent arising from: (a) any breach of investigator's or study team's obligations or representations; or (b) investigator's or study team's negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived therefrom. This obligation 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.

12. ETHICAL CONSIDERATIONS

An application to the University of Pennsylvania Institutional Review Board will be submitted and approved prior to the initiation of any study activities. Dr. Ashare will be responsible for assuring that all staff and participants understand and accept the obligations incurred in undertaking this study in accordance with all applicable regulations; the obligation to obtain informed consent in accordance with 21 CFR Part 50; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56; and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study. In addition, all investigators will be responsible for ensuring that the study is conducted in accordance with the Declaration of Helsinki and that study information is captured in a comprehensive manner and reported according to Good Clinical Practice (GCP).

12.1. Informed Consent

A fully trained study staff member will obtain informed consent using the combined consent and HIPAA form approved by the PENN IRB. This process will take place before study data are collected and prior to any treatment. The consenting process may occur remotely or in-person as part of the Intake session. If completed remotely, subjects will be contacted via Blue Jeans (HIPAA-compliant) for a videoconference or by phone. Reviewing the consent form will be completed using a REDCap survey and a PowerPoint visual. Staff will email or text the survey link to subjects. Whether in person or remote, staff will review the study description, and all study procedures, potential risks, and information about the study medication will be addressed. Subjects will be given the opportunity to read the consent form in full. Following this, subject questions will be answered, and staff will administer comprehension questions to ensure subject understanding. Any incorrect answers will be addressed by the staff member completing consent. If remote, subjects will indicate within the REDCap survey if they wish to participate and will then be prompted to enter their First and Last name and sign the form using their finger or mouse. Subjects who are unable to provide an electronic signature may be mailed a physical version of the consent that must be mailed back to us prior to continuing with the Intake tasks. If needed, staff may also ask subjects to sign a physical version of the form at their first in-person visit for record keeping. Subjects will be able to download their signed version of the form from REDCap, and staff will also download a version to be saved to the electronic regulatory binder on our secure server, or, printed and placed in our physical binder. If in-person, subjects will receive a physical copy of the combined consent and HIPAA form for their records. Subjects will also be given the PI and Study Physician's contact information should they wish to speak to either of them during the course of the study regarding their consent or the study procedures. The consent process will take place in English, there will be no waiting period, no coercion to participate, and all subjects will be considered competent to provide informed consent (i.e., they will be asked if they understand what they are consenting for).

13. RESOURCES NECESSARY FOR CONDUCTING RESEARCH

13.1. Research Staff

Research staff at the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) have successfully conducted similar protocols. Dr. Ashare's research team consists of a Project Manager, Study Coordinators, and Research Assistants who have successfully completed tasks on similar research protocols, including screening potential subjects, scheduling study visits, running Intake Visits and other study sessions, collecting biological samples, overseeing computer tasks, providing smoking cessation behavioral counseling, and data entry and quality assurance. Dr. Ashare (PI) will oversee the research team and provide guidance as needed.

13.2. Study Facilities

This project will be conducted at and through the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA). The CIRNA has successfully conducted similar protocols and has well-developed procedures for staff training, data collection and storage, and study completion. The facilities available for this project include a large and small conference room, individual consulting rooms with computer/internet access, storage rooms, office space for study personnel, and data management facilities. In addition, CIRNA houses two freezers for sample storage. A -80°C freezer is used for long-term sample storage, while a -30°C freezer is utilized for daily access of current sample boxes. These freezers contain temperature and power monitoring sensors which are connected to a Sensaphone alarm system that will contact specific biospecimen staff in the event of an emergency.

If participants require referral for psychological services, information about such programs at 3535 Market Street and/or the Philadelphia area will be provided; we have a form with specific information about such programs already in use in other CIRNA studies.

14. STUDY FINANCES

14.1. Funding Source

This study is financed through a contract with Novo Nordisk Inc.

14.2. Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14.3. Subject Compensation

To reimburse participants for the time and effort needed for completing assessments, participants may earn up to $610, which includes $10 for travel-related expenses at each in-person visit and $5 for each dietary recall. In place of $10/session to cover travel expenses, participants may elect to use a round-trip car ride service (such as Lyft) which will be arranged and paid for in full by the research study. If participants choose to use the ride service, they will not receive $10 for travel reimbursement and their total visit compensation will be up to $365. Participants will receive a reminder call 24-48 hours prior to their study visit to confirm their ride.

The “task completion” compensation will depend on participants arriving on time for scheduled visits. If participants do not follow the study instructions, some or all of the task completion compensation may be withheld. If participants are withdrawn from the study by the investigator during a study visit, they will only be compensated $10 to cover travel costs, unless they have elected to use the ride service. If participants are unable to attend a session in person but still completes the session over the phone, they will receive compensation for task completion but not for travel.

The GreenPhire ClinCard will be the primary form of payment for this study. The ClinCard is a reloadable, pre-paid card for the purposes of compensation. Compensation will be loaded onto the ClinCard within 24 hours of completed visits. Staff may ask participants to provide a Social Security Number, or complete a W-9 for this purpose, after determining eligibility so that a ClinCard can be assigned. Additionally, the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year. ClinCards may be mailed to subjects following the eligibility determination for the study.

Participants may receive a $100 bonus for completing the study. Participants may also receive a $10 bonus for each person successfully referred to the study once their participation has ended, for a maximum of two referrals.

14.4. Traveling via the Ride Service

Participants may elect to use "Roundtrip", which is a car ride service that partners with Lyft to coordinate roundtrip rides to study appointments. Study staff will schedule each ride using participants' first name, last name, and phone number via Roundtrip's HIPAA compliant platform. Participants will receive two reminder calls within 24-48 hours prior to their study visit. The first will serve to confirm their visit, interest in using the ride service, and preferred pickup/drop-off locations. The second will serve to notify participants of their ride's pickup time. If the study staff cannot reach participants by 5pm the day prior to their study visit, their ride will be cancelled. Participants will still be permitted to attend the visit and will receive $10 to cover travel expenses. If participants need to cancel a previously confirmed ride, they must do so by contacting the study staff immediately, preferably by 5pm the day before their appointment. If participants fail to notify study staff within this timeframe, they may no longer be permitted to use the ride service at future study visits.

14.5. Subject Compensation Table

Compensation Schedule							
Week	**Study Visit**	**Task Completion**	**Travel[1]**		**Dietary Recalls**	**Bonus**	**Total**
0	Intake	$20	$10				$30
1	Lab Visit 1	$35	$10		$15		$60
2	Pre-Quit Clinic Visit	$15	$10				$25
3	Pre-Quit Clinic Visit	$15	$10				$25
4	Pre-Quit Clinic Visit	$15	$10				$25
5	Lab Visit 2	$35	$10		$15		$60
6	Monitoring Clinic Visit	$15	$10				$25
7	Monitoring Clinic Visit	$15	$10				$25
8	Monitoring Clinic Visit	$15	$10				$25
10	Monitoring Clinic Visit	$15	$10				$25
12	Monitoring Clinic Visit	$15	$10				$25
14	Monitoring Clinic Visit	$15	$10				$25
18	Monitoring Clinic Visit	$15	$10		$15		$40
22	Monitoring Clinic Visit	$15	$10				$25
26	Monitoring Clinic Visit	$15	$10				$25
32	Monitoring Clinic Visit	$20	$10		$15		$45
32	Completion Bonus					$100	$100
					Study Total:		**$610**
N/A	Referral Bonus					$20^	$20
					Total w/ Referrals		**$630**

Note: [1] Only applies if participants opt to receive $10 travel reimbursement for that visit.
^ Table shows compensation for two successful referrals.

15. PUBLICATION PLAN

We anticipate that data collection will be finished by Month 30 and that analyses and the final study report will be complete by Month 36. A manuscript reporting study results will be submitted for publication at a peer-reviewed journal. In addition, study results will be submitted for presentation at a national or international scientific meeting. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the prior review by and opportunity to comment by the study Sponsor. For the avoidance of doubt, no right of editorial control is provided to study Sponsor. Any investigator involved with this study is obligated to provide the Sponsor with complete test results and all data arising from the performance of the study.

16. APPENDICES

16.1. Table of Study Time Points and Procedures

	Intake	Pre-Quit Period					Monitoring Period									
	Study Week															
Study Procedures		1	2	3	4	5	6*	7	8	10	12	14	18	22	26	32
Medication																
Review Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Symptoms Evaluation Checklist		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[6]
Adverse Events (AEs)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[6]
Liraglutide or Placebo		x[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study Medication Adherence			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Screening																
Informed Consent	x															
Medical History	x															
Demographics	x															
Brief Physical Examination	x															
MINI	x															
C-SSRS, CES-D	x[7]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]	x[5]
Height	x															
Urine Drug Screen	x	x				x										
Urine Pregnancy Test	x[2]	x[2]	x[29]	x[29]	x[29]	x[2]	x[29]	x[29]	x[29]	x[29]	x[29]	x[29]	x[2]	x[9 2]	x[29]	x[2]
Blood Pressure, Heart Rate	x	x	x[9]	x[9]	x[9]	x	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x	x[9]	x[9]	x
Blood Glucose Monitoring	x	x	x[9]	x[9]	x[9]	x	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x	x[9]	x[9]	x
Outcome Measures																
Body Weight, CO	x	x	x[9]	x[9]	x[9]	x	x[9]	x[9]	x[9]	x[9]	x[9]	x[9]	x	x[9]	x[9]	x
Smoking Rate & Alcohol Use (TLFB)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[6]
Saliva Sample Collection								x[3]								x[3]
Blood Sample Collection	x	x				x							x			x
Standardized Questionnaires																
Shipley-2	x															
Smoking & Alcohol History, FTND, AUDIT	x															
CES, SQ (Last 7 Days)	x	x				x										
Mood (PANAS), MNWS, QSU-B		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Activity (PAR), Weight Concerns		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Bipolar Measures (MADRS, Y-MRS)	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]	x[8]
Impact of COVID-19 on Smoking Survey	x														x	
Food-Related Measures																
Food Craving Questionnaire-Trait	x												x			x
Dutch Eating Behavior Questionnaire	x												x			x
Pre-FCQ-S	x															
FCQ-S (with food computer task)		x				x										
Food Intake (24-Hr Dietary Recalls)		x[4]				x[4]							x[4]			x[4]
Smoking Cessation Counseling																
Pre-Quit Counseling Session						x										
Target Quit Date Session							x									
Booster Counseling Session								x	x	x	x		x		x	

MINI = Mini International Neuropsychiatric Interview; C-SSRS = Columbia-Suicide Severity Rating Scale; CES-D = Center for Epidemiological Studies Depression scale; TLFB = Timeline Follow Back; CO = Carbon Monoxide reading; FTND = Fagerstrom Test for Nicotine Dependence; AUDIT = Alcohol Use Disorders Identification Test; CES = Cigarette Evaluation Scale; SQ = Sensory Questionnaire; PANAS = Positive and Negative Affect Schedule; MNWS = Minnesota Nicotine Withdrawal Scale; QSU-B = Questionnaire of Smoking Urges - Brief; PAR = Physical Activity Recall; Pre-FCQ-S = Pre-Food Craving Questionnaire-State, FCQ-S = Food Craving Questionnaire-State
***** = Target Quit Date; [1] = Participants will be randomized to receive either liraglutide or placebo; [2] = Female participants only; [3] = Based on smoking behavior, participants may be asked to provide a saliva sample; [4] = Three 24-hour dietary recalls will be completed over the phone prior to this visit (+ 7 days); [5] = If participants score 16+ on the CES-D, the Since Last Visit C-SSRS will be administered; [6] = 4 weeks after the Week 32 visit, participants will be contacted by phone to complete a TLFB, Symptoms Evaluation Checklist, and follow up on ongoing AEs; [7] = Baseline/Screening C-SSRS only. [8] = Only administered for participants with bipolar disorder. [9] = Measure may not be completed if session is conducted remotely.

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