

NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template

Effects of Semaglutide on Nicotine Intake and Smoking Lapse

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.2	Increased BMI range for eligible participants from 25-35 to 23+, and removed eligibility criterion related to TSH values (thyroid disease will still be exclusionary).	Adjustments are intended to make eligibility less restrictive, and were made in consultation with the study physician.

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STATEMENT OF COMPLIANCE

(1) The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Effects of Semaglutide on Nicotine Intake and Smoking Lapse

Study Description: This is an early-Phase II human laboratory trial using a randomized, placebo-controlled, dose-ranging design to investigate the effects of semaglutide (Ozempic®), a GLP-1 receptor agonist, on laboratory nicotine responses, reinstatement, self-administration, naturalistic cigarette consumption, and weight loss in regular smokers. Participants will attend weekly visits while semaglutide dosage is increased to 1.0mg over a period of 10 weeks. At scheduled intervals, participants will attend 2 laboratory sessions involving a validated smoking lapse procedure to characterize medication effects on nicotine reinstatement and laboratory self-administration.

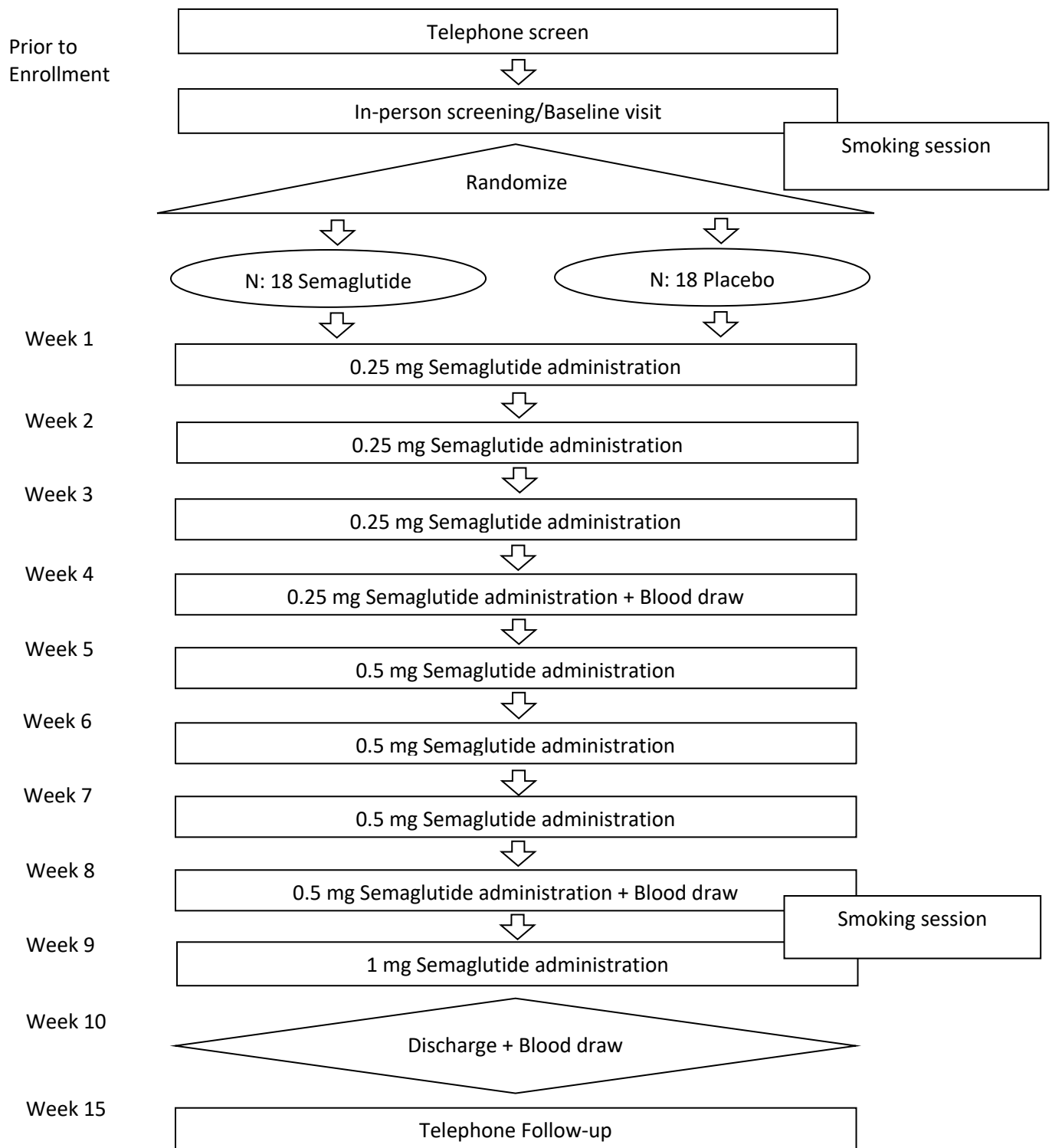
Objectives: Primary Objective: To examine effects of semaglutide vs. placebo on nicotine reinstatement and self-administration under laboratory conditions.

Secondary Objectives: To examine medication vs. placebo group differences in 1) changes in naturalistic cigarette consumption, and 2) changes in body weight over the course of the treatment period.

Tertiary Objectives: To generate preliminary data on medication effects on laboratory responses to nicotine, and cue-induced craving among regular smokers during treatment with semaglutide.

Endpoints:	<p>Primary Endpoint: Changes in 1) nicotine reinstatement (i.e., minutes of resistance to smoking reinstatement), and 2) nicotine self-administration (i.e., cigarettes consumed during ad libitum smoking). The comparison of interest is the difference between medication and placebo groups in the change in laboratory consumption between baseline and the maintenance dose of 0.5mg. (i.e., treatment x time interaction).</p> <p>Secondary Endpoints: Number of cigarettes consumed per day during the treatment phase (Weeks 0-10) as measured by a daily diary survey, and change in body weight during treatment. Within-subjects changes in these outcomes will be compared as a function of medication condition.</p> <p>Tertiary Endpoints: Laboratory measures of subjective responses to cigarette consumption, assessed by the Modified Cigarette Evaluation Scale and Drug Effects Questionnaire, and responses to a cue-induced craving task.</p>
Study Population:	Participants with at least moderate nicotine dependence (based on smoking 5+ cigarettes daily) will be enrolled (N=36). Participants will be recruited from the Triangle area (community and hospital settings). Participants must be non-treatment-seeking
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	This is a single-site study (UNC-Chapel Hill). The project will be based at the Bowles Center for Alcohol studies and the Department of Psychiatry, with clinical operations taking place at Eastowne Clinical Research Unit and CTRC.
Description of Study Intervention:	Semaglutide (Ozempic®) will be administered according to the FDA-approved schedule, which begins with a starting dose of 0.25mg once per week for four weeks. At week five, dosage is increased to 0.5mg/week for a subsequent four weeks (maintenance dose). Following four weeks at the maintenance dose, dosage can be increased further (1.0mg) provided the patient has tolerated the medication. Semaglutide is administered subcutaneously via the Ozempic® pen, a cartridge-based device that calibrates medication delivery. The placebo condition will consist of weekly sham doses, which will involve a brief needle insertion (without an injection).
Study Duration:	Up to 13 months.
Participant Duration:	25-35 hours (including in-person visits and remote questionnaires) over a period of approximately 15 weeks.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Telephone Screening	Screening/Baseline	Study Visit 1 - 3 Target Day 7, 14, 21	Study Visit 4 Target Day 28	Study Visit 5 - 7 Target Day 35, 42, 49	Study Visit 8 Target Day 56	Study Visit 9 Target Day 63	Discharge Target Day 70	Telephone follow-up Target Day 77, 105	Smoking Challenge Target Day -10, 58
Procedures and Questionnaires										
Telephone screening	X									
Administer 0.25 mg Semaglutide or placebo			X	X						
Administer 0.5 mg Semaglutide or placebo					X	X				
Administer 1.0 mg Semaglutide or placebo							X			
Urine Drug Screen		X								X
Expired carbon monoxide (CO)		X	X	X	X	X	X	X		X
Locator		X								
Timeline Follow-Back (TLFB)		X	X	X	X	X	X	X		
Blood draw		X		X		X		X		
Blood glucose – finger prick		X	X		X		X			X
Pregnancy (females only)		X	X	X	X	X	X	X		X
Weight/BMI		X	X	X	X	X	X	X		X
Height		X								
Vitals (HR, BP)		X	X	X	X	X	X	X		X
Temperature		X								
Demographics Form		X								
SCID for DSM-5 (substance use)		X								
MINI Neuropsychiatric Interview		X								
Medical and Substance Use History Interviews		X								
Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X
Alcohol Use Disorder Identification Test (AUDIT)		X								
Alcohol, Cigarette, and Food Purchase Test		X								X
Self-Report of the Effects of Alcohol Questionnaire (SRE)		X								
Fagerstrom Test for Nicotine Dependence (FTND)		X								
Nicotine Dependence Syndrome Scale (NDSS)		X								
Penn Alcohol Craving Scale (PACS)		X	X	X	X	X	X	X		X
Tiffany Questionnaire of Smoking Urges (TQSU)		X	X	X	X	X	X	X		X
Wisconsin Smoking Withdrawal Scale (WSWS)		X	X	X	X	X	X	X		X
Alcohol and Smoking Contemplation		X	X	X	X	X	X	X		
Three Factor Eating Questionnaire (TFEQ)		X	X	X	X	X	X	X		X
Monetary Choice Questionnaire (MCQ)		X	X	X	X	X	X	X		X
Cigarette Abstinence Self-Efficacy (CASE)		X	X	X	X	X	X	X		X
Alcohol Abstinence Self-Efficacy (AASE)		X	X	X	X	X	X	X		X
Inventory of Drinking Situations (IDS)		X								
Impaired Control Scale (ICS)		X								
Barratt Impulsivity Scale (BIS-11)		X								
UPPS Impulsive Behavior Scale (UPPS)		X								
Systematic Assessment for Treatment Emergent Effects (SAFTEE)		X	X	X	X	X	X	X	X	X
Reward Based Eating Drive Scale (R-BEDS)		X	X	X	X	X	X	X		X
Simplified Nutritional Appetite Questionnaire (SNAQ)		X	X	X	X	X	X	X		X
Control of Eating Questionnaire (CEQ)		X	X	X	X	X	X	X		X
Wisconsin Inventory of Smoking Dependence Motives (WISDM)		X								
Sweet Taste Preference Test		X								X

Center for Epidemiological Studies Depression Scale (CES-D)		X							
Reward Probability Index – Environmental Reward Observation Scale (RPI-EROS)		X							
Toronto Alexithymia Scale (TAS-20)		X							
Profile of Mood States – Short Form (POMS-SF)									X
Cigarette Evaluation Questionnaire (CEQ)									X
Drug Effects Questionnaire (DEQ)									X
Peak Provoked Craving (PPC)							X		X
Obsessive-Compulsive Drinking Scale		X							
Graded Pain Scale		X							

2 INTRODUCTION

2.1 STUDY RATIONALE

Despite declines in smoking prevalence in the United States, the likelihood of successfully quitting smoking has not improved [1, 2]. Roughly three in four smokers report the desire to quit, and up to half report past-year quit attempts [3, 4]. However, only 4-5% of smokers achieve sustained cessation in a given year [4], with relapse typically occurring within 5-10 days of a quit attempt [5, 6]. While the introduction of varenicline in 2006 was followed by marginally greater rates of pharmacotherapy utilization, no appreciable changes in sustained cessation have been observed since [4]. Given only three FDA-approved smoking cessation aids (varenicline, bupropion, and nicotine replacement therapy), advancing novel smoking cessation therapies is a critical aim [1, 7]. In principle, establishing a repertoire of medications will improve options for combination and personalized treatments [8-10]. Because the three FDA-approved smoking cessation medications each act on nicotinic receptors, identifying novel therapies with alternate pharmacological targets is a key priority [1, 7].

Glucagon-like peptide 1 (GLP-1) is an incretin hormone, produced both peripherally (in the intestines) and centrally (e.g., in the hindbrain) [11]. GLP-1 is stimulated following food consumption and stimulates satiety and decreases in blood glucose. As a peptide with both hormonal and neurotransmitter functions, GLP-1 plays a role in the "gut-brain axis," which has recently been invoked as a target for addiction treatment [12]. GLP-1 agonist medications were designed to mimic the function of the endogenous GLP-1 peptide, with the benefit of a much longer half-life than endogenous GLP-1. Based on their glucose-lowering and appetite-reducing properties, GLP-1 agonists were developed as anti-diabetic therapies. Several GLP-1 agonists (e.g., exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide,) are now in widespread use as treatments for type II diabetes (T2D). These medications have also proven efficacious for weight loss, reducing glycated hemoglobin (HbA1c), and reducing risk for some cardiovascular events [11]. Recently, a large-scale, multi-site study of semaglutide demonstrated substantial reductions in body weight in adults with overweight or obesity [13].

Cigarette smoking and obesity are two of the foremost contributors to preventable health burdens globally. Moreover, these conditions often co-occur. Among numerous barriers to smoking cessation, a commonly cited clinical barrier is patient concerns about weight gain following cessation. Therefore, therapies that can simultaneously aid in smoking cessation while promoting weight loss could be particularly valuable as adjunctive therapies to standard treatment approaches, such as nicotine replacement therapy (NRT). The aim of this project is to conduct an initial Phase II study of semaglutide in dependent smokers who are not actively trying to quit smoking. Using a validated smoking lapse paradigm, we will investigate the ability of semaglutide to reduce nicotine reinstatement and number of

cigarettes consumed under laboratory conditions. We will also investigate medication effects on weight loss among smokers during treatment with semaglutide over a 10-week treatment period, in order to inform future studies in smokers with weight concerns.

Of note, GLP-1 agonists require subcutaneous administration, typically by way of a pre-filled medication cartridge with a micro-needle attachment, which allows for easy self-administration in the home without assistance from medical staff. Semaglutide is a recently approved (2017) FDA-approved GLP-1 agonist. Semaglutide was initially approved in a weekly subcutaneous formulation (Ozempic®) with a maximum dose of 1mg/week. A new oral formulation of semaglutide was approved by the FDA in 2019, making semaglutide the first drug in its class to be available in both subcutaneous and oral formulations. More recently (June 2021), the FDA approved Wegovy®. Similar to Ozempic®, Wegovy® is a weekly subcutaneous formulation, but utilizes a higher maximum dose (2.4mg/week) for the indication of overweight/obesity. Semaglutide is prescribed at a starting dose of 0.25mg for 4 weeks, followed by 0.5mg for 4 weeks, followed by further increase up to either 1mg (Ozempic®) or 2.4mg (Wegovy®).

2.2 BACKGROUND

Accumulating evidence from preclinical studies suggests that GLP-1 agonists reduce intake and/or reinstatement of addictive drugs in animal models. In a recent review of 17 preclinical studies [14], all studies reported significant effects of GLP-1 agonists on indices of drug motivation and intake [12, 14]. Notably, the effects of GLP-1 agonists on drug intake appear to extend to several addictive drugs, including nicotine [15]. These findings have led to recent studies aiming to investigate the efficacy of GLP-1 agonists as candidate therapies for addiction. Although several human trials are underway in various countries, no RCTs have been published to date, and human data on the efficacy of GLP-1 agonists for reducing drug intake in substance-using populations is needed.

Although the precise mechanisms mediating the effects of GLP-1 agonists on addiction-related behaviors remain to be clarified, it has been suggested that cholinergic-dopaminergic pathways are involved in altering the reward value of addictive substances following exposure to GLP-1 agonists [12]. Additionally (and relevant to the original goals of this R21 to target the serotonin system using lorcaserin), GLP-1 agonists appear to exert their effects in part by way of interactions with the serotonin (5-HT) system, including interactions with 5-HT_{2C} receptors. Specifically, GLP-1 agonists appear to induce serotonin release, and serotonin signaling appears critical to the efficacy of the medications [16, 17]. Evidence also suggests that 5-HT_{2C} receptors appear necessary for the efficacy and satiety-inducing effects of GLP-1 agonists [18, 19].

Of the approved FDA-approved GLP-1 agonists, most preclinical studies of addiction-related phenotypes have focused on exenatide, an older GLP-1 agonist first approved in 2005. As noted, semaglutide is the newest GLP-1 agonist and the first available in both subcutaneous and oral formulations. Some evidence suggests superiority of semaglutide relative to other GLP-1 agonists with respect to efficacy for glycemic control [20]. Also, as noted, a recent large-scale trial showed striking reductions in weight during long-term treatment with higher doses of semaglutide [13]. Given that post-cessation weight gain is a key deterrent for many smokers to remain quit, GLP-1 agonists like semaglutide could be an important adjunct to traditional smoking cessation therapies.

Human laboratory methods for pharmacotherapy development

Human laboratory studies play a pivotal role in drug development by providing an efficient, cost-effective “bridge” between preclinical studies and full-scale randomized trials [21-28]. By allowing efficient cross-validation of both preclinical and Phase III results, human experimental studies serve a cornerstone role in translational drug development [7, 21, 22, 29]. An ancillary advantage of these studies is the ability to test putative mechanisms of pharmacotherapy effects under controlled experimental conditions [26]. As noted, clarifying treatment mechanisms is a critical goal that ultimately informs treatment design, and can also inform selection of clinical endpoints for Phase III trials [21]. Notably, most candidate SUD medications are tested in Phase III trials without prior or subsequent study in human laboratory models [21].

Importantly, recent reviews have also highlighted areas in which laboratory studies can be improved. First, many laboratory studies are limited by a sole focus on self-report outcomes (e.g., craving), which lack a direct analogue in animal models [30, 31]. Relative to self-report outcomes, drug *self-administration* outcomes appear more sensitive to pharmacotherapy effects, and may improve consistency in findings across preclinical and human studies [21]. Additionally, self-reported craving - while undoubtedly a clinically important construct - is neither necessary nor sufficient for self-administration, supporting the need to prioritize objective self-administration outcomes [32]. Another limitation of most human lab studies concerns their discordance with Phase III trials in terms of sample characteristics. A key limitation, as highlighted in a recent systematic review, is that human laboratory studies of smoking pharmacotherapy typically recruit non-motivated smokers, limiting comparisons with Phase III trials [29]. Importantly, evidence shows that recruiting non-motivated smokers undermines the ability to detect medication effects, whereas recruiting smokers with some motivation to quit (even if not engaged in an active quit attempt) improves effect sizes in medication screening trials [24].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Semaglutide (Ozempic®) received FDA approval in 2017 for use as an adjunct to diet and exercise to achieve glycemic control in adults with type 2 diabetes mellitus (T2D). Semaglutide received FDA approval based on the results of 25 completed trials with the goal of providing results that would be applicable to a broad type II diabetes (T2D) population, including the elderly, patients with renal impairment, and patients at high cardiovascular risk. These trials involved > 9,300 participants, of whom >5,700 were treated with semaglutide. In these trials, treatment with semaglutide alone was efficacious for reduction in hemoglobin A1C (HbA1c) below 7% (e.g., 73% of participants had HbA1c <7% at week 30, compared to 28% of placebo-treated patients). Significant body weight reductions were also reported, with the weight loss achieved at end-of-treatment ranging from -1.43 to -4.28 kg (corresponding to 2.3–4.9%). Weight reductions were evident after 4 weeks of treatment, and persisted up to 104 weeks [75]. The peak plasma concentration of semaglutide is reached 1-3 days post-dose. Steady-state exposure is achieved following 4-5 weeks of once-weekly administration, and elimination half-life is approximately 1 week.

Risks related to medication. The most commonly reported side effects/adverse events (AEs) are gastrointestinal, with nausea being the most frequently reported symptom. The majority of reports of nausea (0.5 mg dose vs placebo; 15.3 vs. 6.1%), vomiting (5.0 vs 2.3%), and/or diarrhea (8.5 vs 1.9%) occur shortly following a dose escalation. Abdominal pain (7.3 vs 4.6%) and constipation (5.0 vs 1.5%)

were also reported [76]. In studies ranging from 30-56 weeks in duration, the discontinuation rate due to these gastrointestinal AEs was ranged from 5-13%, with this number increasing during longer treatment durations [77].

Rarer AEs (occurring at a frequency of <5%) included symptomatic hypoglycemia (≤ 70 mg/dL glucose threshold), which occurred in 1.6% of semaglutide-treated participants versus 0% placebo participants; dyspepsia (3.5 vs 1.9%); eructation (2.7 vs 0%); and gastroesophageal reflux disease (1.9 vs 0%). In placebo-controlled trials, injection site reactions (e.g., discomfort, erythema) were reported in only 0.2% of semaglutide-treated patients, suggesting good tolerability of subcutaneous administration. Patients exposed to semaglutide had a mean increase from baseline in amylase of 13% and lipase of 22%. Cholelithiasis was reported in 1.5% of treated patients. The 0.5 mg dose resulted in a mean increase in heart rate of 2 to 3 beats per minute, while there was a mean decrease in heart rate of 0.3 beats per minute in placebo-treated patients. Hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists. [76]. Other adverse reactions with a frequency of >0.4% associated with semaglutide include fatigue, dysgeusia and dizziness [76].

Rodent studies have shown an increase in the incidence of thyroid C-cell tumors after lifetime exposure of semaglutide at clinically relevant plasma levels. However, several studies in T2D patients taking GLP-1R agonists have shown no increase in neoplasm risk, even after several years of use [78]. Nevertheless, a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B is considered a potential risk factor for taking the medication, and will be an exclusionary criterion.

In a 2-year trial, acute pancreatitis was observed in 8 semaglutide-treated patients (0.27 cases per 100 patient years) and 10 placebo-treated patients (0.33 cases per 100 patient years). One case of chronic pancreatitis was confirmed in a semaglutide-treated patient. History of pancreatitis will be an exclusion factor, and study participants receiving semaglutide will be observed for signs and symptoms of pancreatitis (via blood monitoring of serum amylase and lipase). If pancreatitis is suspected, semaglutide will be discontinued, and appropriate management recommended.

Other rare events include postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients receiving long-term treatment with GLP-1 receptor agonists. Some of these events have been reported in patients without known underlying renal disease. Most of these events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Therefore, we will monitor renal function when initiating or escalating doses of semaglutide in patients reporting severe adverse gastrointestinal reactions.

Although most safety data on semaglutide comes from trials with T2D participants, there are now a number of randomized trials underway examining GLP-1 receptor agonists in participants with substance use disorder, including trials on tobacco, cocaine, alcohol, cannabis, and opioids. A full list of registered randomized trials can be found by searching for “GLP-1” at ClinicalTrials.gov. The use of a short-term medication screening protocol (lasting roughly 10 weeks) will provide an opportunity to demonstrate tolerability and generate data on side effect profiles in this population while minimizing any risks associated with longer-term medication exposure.

Risks Related to Questionnaire and Interview Assessments. There may be potential risks associated with assessment procedures. Participants may find the battery of psychiatric and psychological assessments tedious or intrusive. Participants may experience discomfort resulting from questions about personal histories or substance use patterns.

Participation in Smoking Sessions. Other potential risks include typical risks related to participation in smoking sessions. For example, it is possible that participants may experience dizziness/nausea from smoking. However, given our focus on dependent smokers, these risks are likely low. Our group has considerable experience with human laboratory studies involving drug administration and self-administration procedures [80-84], and the safety precautions required in these studies. Additionally, by focusing on non-treatment seekers we will minimize ethical concerns about smoking in the laboratory setting.

Risks Related to DNA Collection. The purpose of collecting saliva for DNA in this study is to allow secondary analyses to examine whether medication effects might be different according to certain genetic factors. These analyses may also focus on genetic factors potentially associated with drug use or related behaviors, such as nicotine and alcohol metabolism, dopaminergic function, or impulsivity. Potential risks associated with DNA collection involve potential identification, and there may be risks with genetic (DNA) tests that are as yet unknown. Genes may be shown at some point in the future to be related to mental illnesses or tendency to addiction. Samples will be labeled with participant ID only, and analyzed at an outside laboratory. Samples will be de-identified and links with participant identifiers will be broken upon completion of the analyses. We will not conduct any whole genome sequencing of the DNA samples. Additionally, the consent form will state that participants have the option to opt out of DNA collection, and to request that their samples are destroyed at any time during the study. Participants will not receive any feedback from any of the genetic tests from study staff.

2.3.2 KNOWN POTENTIAL BENEFITS

The participants in this study are not expected to benefit directly from their participation. However, the knowledge gained from this study could lead to a better understanding of a medication with potential to treat nicotine addiction, and potentially other substance use disorders.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Given the vast health implications of substance use disorder and the currently limited array of effective medications, it is imperative to pursue novel pharmacotherapeutic options. A key strategy in this regard is to “repurpose” medications that are already approved (and have proven safe) in the context of other health conditions. Given the sizable amount of research on GLP-1 receptor agonists in other clinical populations, coupled with preclinical evidence that these medications reduce motivation for alcohol, nicotine, and other drugs, evaluating this medication class in the proposed population is warranted. If GLP-1 receptor agonists prove useful for reducing smoking while also reducing weight, they could have promise a therapeutic option for smokers with obesity, smokers with concerns about weight gain during smoking cessation. From this standpoint, the risk/benefit profile for testing semaglutide in a population of non-diabetic participants is favorable.

Although we anticipate the risk of adverse events to be low based on the safety profile of the medication, gradual dose escalation, and relatively short duration of treatment, several steps will be taken to track and report medication-related side effects. As described further in later sections of this application, participants will be monitored regularly by virtue of attending weekly lab visits for medication delivery, at which side effects will be assessed and clinical lab results monitored. Participants will be given a contact number for study medical staff in case of serious emergent side effects, (and

instructed to seek medical attention in the event of any serious side effects), and participants will be contacted by phone shortly after dose escalations to monitor symptoms. We expect some participants to experience nausea shortly following dose escalations, but that these symptoms will usually be transient.

Given the focus on a non-diabetic population, we will be particularly vigilant in monitoring changes in body weight and blood glucose, and will exclude participants at the outset with body weight or blood glucose levels below normal range, based on physician judgement. We will carefully monitor participants with glucose tests and weight measurements at regularly study visits (see schedule of activities table), and will instruct participants to be vigilant for potential symptoms of hypoglycemia. Periodic blood tests to measure fasting glucose, fasting insulin, serum lipase and amylase, and serum calcitonin will occur at baseline and regularly thereafter (i.e., at visits prior to dose escalations). All adverse events will be documented and reported in accordance with relevant policies, and the regulations of NIH. We have enlisted the TraCS DSMB to assist with safety monitoring of the study. The board will convene at the beginning of the study and at scheduled points to review study progress and safety data, and to review any SAEs and considerations related to stopping rules (described further below).

Considering the use of an FDA approved medication that has been deemed safe in the context of chronic administration for glycemic control, the risks related to medication use in this short-term screening trial are acceptable in comparison to the potential benefits of the proposed research (i.e., demonstrating potential efficacy of a new medication for smoking cessation).

Risks Related to Smoking Sessions. As noted, participants could experience transient nausea or dizziness while smoking. However, our recruitment of dependent smokers likely minimizes these risks. Participants may experience boredom or fatigue during the 2-hour smoking sessions. Our recruitment of non-treatment-seeking, dependent smokers is designed to minimize risks and ethical concerns associated with the laboratory smoking procedure.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To examine effects of semaglutide vs. placebo on nicotine reinstatement and self-administration under laboratory conditions.	The primary outcomes for the human laboratory sessions consist of 1) nicotine reinstatement (i.e., minutes of resistance to smoking reinstatement), and 2) nicotine self-administration (i.e., cigarettes consumed during ad libitum smoking). The comparison of interest is the difference between medication and placebo groups in the change in laboratory outcomes between baseline and the maintenance dose of 0.5mg.	Primary: This simulated smoking lapse procedure was developed by McKee, who is a consultant on this project. The McKee paradigm is the only validated laboratory procedure that models smoking reinstatement and self-administration concurrently. These primary outcomes are selected because they reflect objectively defined behaviors analogous to those reported in preclinical studies. Laboratory assays of nicotine reinstatement and self-administration have been used in prior human laboratory studies to screen candidate medications,

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		allowing comparisons with effect sizes for other medications.
Secondary		
To examine group differences in 1) naturalistic smoking behaviors over the course, and 2) weight loss over the course of the 10-week treatment period.	<p>Number of cigarettes consumed per day during the treatment phase (Weeks 0-10), as measured by a daily diary report.</p> <p>Changes in body weight, assessed weekly over the treatment period.</p>	<p>Measures of cigarettes per day are selected to afford greater power for modeling change in consumption over the treatment period. Note that these outcomes are considered secondary because this Phase II trial involves non-treatment-seeking participants who are not attempting to reduce cigarette smoking.</p> <p>GLP-1 receptor agonists lower HbA1c and body weight in indicated populations (e.g., Type II diabetes). Given high co-occurrence of obesity and tobacco use disorder, reporting whether medication is associated with these reductions in the present sample is clinically relevant.</p>
Tertiary/Exploratory		
To examine group differences in subjective responses to cigarette smoking and cue exposure.	<p>Laboratory measures of subjective response, assessed by the Modified Cigarette Evaluation Scale and Drug Effects Questionnaire. The Positive and Negative Affect Scale will also assess change in mood.</p> <p>Cue-elicited craving assessed using self-report measures of craving during a cue induction procedure, peak provoked craving (PPC).</p> <p>Similar to the primary outcome, secondary outcome analyses will examine medication vs. placebo group differences in within-subjects changes in these outcomes over time (0mg to 0.5mg).</p>	<p>Laboratory measures of cigarette subjective response are clinically valid indicators of drug motivation, and are demonstrated to be sensitive to medication effects. Investigating these outcomes under controlled conditions will allow us to test for a medication “signal” on measures of nicotine reward.</p> <p>Human studies of the effects of GLP-1 receptor agonists on cue-elicited drug craving have not been reported. As an exploratory aim, we will also utilize an established cue reactivity task to assess peak provoked craving (PPC). This procedure, which involves assessing craving during a cue exposure task (lighting a cigarette and attending to cues) while in a period of short-term abstinence, has been demonstrated to reliably induce acute craving.</p>

4 STUDY DESIGN

4.1 OVERALL DESIGN

Overview of Study Design.

The aim of this proposal is to translate preclinical findings on the therapeutic potential of GLP-1 agonists by conducting an early-Phase II investigation of semaglutide in dependent smokers. The project will include a focus on human laboratory outcomes, including a validated human laboratory analogue of smoking lapse and self-administration. Daily measurements of naturalistic smoking, and weight reduction during the trial, will be examined as secondary outcomes. Overall, this study aims to generate initial data on the efficacy of semaglutide in a sample of smokers who are not actively engaged in a quit attempt.

This is a single-site, Phase II, two-arm, double-blind (participants, outcome assessors), randomized, placebo-controlled, dose-ranging study. Following a baseline assessment, eligible participants will be randomized to medication or placebo conditions by the IDS staff at a 1:1 ratio. The treatment period will be approximately 10 weeks, taking into account the dose escalation necessary for this medication. Those randomized to semaglutide will receive 0.25mg/week for 4 weeks (Weeks 1-4), 0.5mg/week for 4 weeks (Weeks 5-8). Provided that participants have tolerated the medication adequately, participants will receive a final, single dose of 1.0mg (Week 9), and will return for a discharge lab visit with repeat lab tests at Week 10, followed by a final monitoring assessment by phone scheduled approximately 6 weeks after the last medication dose (Week 15). Those in the placebo condition will receive sham placebo administration at each visit (described in further detail in later sections). Participants will attend weekly visits at Eastowne CRU or CTRC to receive medication or placebo doses.

In addition to the medication visits, participants will be asked to attend two laboratory visits involving cigarette smoking (one prior to the first medication visit and one during the 0.5mg treatment phase). These sessions are designed to assess changes in nicotine reinstatement and *ad libitum* smoking over the course of the treatment period. Laboratory sessions are described in further detail below. Measurements of naturalistic cigarette use will also be recorded throughout the treatment period. These assessments will be captured using a daily diary that will be provided to participants. Participants will receive an automated text message daily via Phone.com as a reminder to complete the diary. Additional self-report measures of substance use will be collected at study visits.

As summarized above, the primary objectives are to examine whether treatment with semaglutide alters nicotine self-administration and reinstatement (primary outcomes), as well as body weight and laboratory measures of nicotine responses (secondary outcomes). We hypothesize that semaglutide treatment (versus placebo) will be associated with reductions in nicotine self-administration and reinstatement during a laboratory session conducted at the Ozempic® maintenance dose of 0.5mg (relative to a session conducted at baseline). Each dosage increase will be contingent on the participant tolerating the current dose without significant side effects.

The primary outcomes for this trial will be assessed during exposure to the standard Ozempic® maintenance dose (.5mg). While an extended treatment phase at the 1.0mg dose is beyond the scope of this small-scale trial, the inclusion of a brief (1-week) phase at 1.0mg is designed to provide initial data on tolerability and any changes on selected secondary outcomes (i.e., cigarettes per day). Capturing these data will help to support feasibility and pilot data for subsequent funding proposals.

Secondary objectives include examining changes in naturalistic cigarette smoking during the treatment period and body weight during the trial. Although participants will not be attempting to reduce smoking in this trial, it is hypothesized that treatment with semaglutide will result in reductions in nicotine consumption (cigarettes per day) over the course of the treatment period. Tertiary/exploratory

outcomes include examining group differences in changes in subjective responses to cigarette smoking and cue-elicited craving from placebo to 0.5mg phases.

In total, participation in this study is estimated to take roughly 25-35 hours of combined time over a period of approximately 16 weeks. This includes a screening and baseline visit (up to 4 hours), up to 9 subsequent laboratory visits for medication administration and side effects monitoring (up to 1 hour each), and a final discharge visit (Week 10), and final telephone check-in (Week 15). If necessary for safety reasons, (e.g., based on lab results), participants may be asked to attend (unplanned) visit(s) for follow-up labs at the discretion of the study physician. Participants will also complete two visits involving nicotine self-administration over the course of Weeks 0-10; these sessions may last up to 3-4 hours each. Participants also will receive calls from staff on Day 2 or 3 of each medication titration phase (placebo, 0.25mg, 0.5mg, 1.0mg) to check in on side effects (10 minutes per call), and will be asked to complete brief daily questionnaires via a daily diary with reminders sent via daily text message prompt (1-2 minutes per day).

A detailed summary of study procedures is provided below.

Detailed Study Procedures.

Following initial recruitment (described in section 5.5), participants will be asked to complete the following procedures:

a) Telephone screen

Initial screening will be conducted by telephone by trained research staff and will assess participant's cigarette use, other drug use, medications, and basic medical inclusion/exclusion factors. Potential participants will be given a brief description of the study. The initial telephone screen is estimated to take roughly 15-30 minutes. Contact information will be collected from interested callers who pass the initial screen. Following the initial screen, participants will proceed to be booked for an informed consent and baseline interview session. The informed consent procedures will be conducted remotely using a HIPAA-compliant virtual meeting platform (e.g., Webex, Zoom) and DocuSign. Depending on participant and staff availability, the phone screening and informed consent/baseline interview can happen on the same day (after the screening call) or at a future date.

b) Screening and Baseline Data Collection Visits

At the informed consent session, a member of the research staff will review the study procedures and carry out informed consent procedures (including electronic signature via DocuSign) prior to proceeding to the baseline interview. Following informed consent, the staff member will conduct a semi-structured interview to assess inclusion/exclusion criteria. A research assistant will use a structured interview to measure diagnostic and substance use screening criteria; inclusion/exclusion factors related to medical history will also be assessed (see criteria listed above). The Structured Clinical Interview for DSM-V [53] will be used to assess substance use disorder symptoms. History of other psychiatric diagnoses and medication use will be assessed via self-report. The research assistant will also collect information on demographic factors, criteria related to current medical status and medications, current alcohol, tobacco and other substance use (see "Phone Screen" document), as well as substance use disorder symptoms (via select modules from the SCID interview) and symptoms other

psychiatric symptoms (using the MINI screening module). Participants who appear eligible will be booked for an in-person visit, which will take place at the Eastowne CRU or the laboratory site (Medical Wings C), with some procedures (e.g., blood draw) booked at CTRC as necessary.

The in-person screening/baseline visit will include a brief review of informed consent to answer any additional questions, and a brief review of self-report and interview questions from the remote screening session. The Timeline Follow-Back (TLFB) [54] will be used to assess alcohol, cigarette and other drug use in the 90 days prior.

Participants who remain eligible after the interview will complete vitals and measurements (HR, BP, height, weight, temp), and a measure of expired alveolar carbon monoxide (CO). Additionally, participants will provide a urine sample and complete a blood draw (up to 70-80 ml) for a comprehensive metabolic panel (e.g., Na, K, Cl, CO₂, BUN, Creatinine, Glucose, Calcium, Albumin, Total protein, Total bilirubin, AST, ALT, Alk Phos), baseline measure of HbA1c, baseline measure of nicotine metabolites (e.g., 3HC, COT), serum amylase and lipase, and complete blood count (e.g., Auto WBC, Corrected WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, MPV, Platelet). These procedures will be conducted by the research assistant, and the baseline blood draw will be taken by a team member with phlebotomy training. If there is no team member with phlebotomy training available that day, the blood draw may also be booked at CTRC. If needed, the blood draw and other baseline procedures may be booked as separate visits. On the day of the visit that includes the blood draw, participants will be instructed to arrive fasting for 12 hours (to allow for assessment of baseline HbA1c and lipids). If participants are not able to arrive fasting for the baseline session, the fasting lipids sample may be deferred or completed at the next possible visit. Blood samples will be sent to McClendon laboratory for testing. A portion of the blood sample (de-identified) will also be stored (Thurston Bowles building and Neurosciences Research Building) for subsequent analysis (e.g., nicotine metabolites and blood neutrophils, which are affected by cigarette smoking). Neutrophil analyses will be conducted by Dr. Robert Tarran's lab.). The urine sample will be used to test for the presence of several drugs (for example, heroin, cocaine, methamphetamines, opiates). (For females, the test will include a pregnancy screen.) If a participant tests positive for drugs other than cannabis (or if females screen positive for pregnancy), the participant will be excluded from the study.

Participants will complete baseline questionnaires, which will be collected on paper. A Demographic Screening Questionnaire will assess basic demographic factors (e.g., age, education, income). A Locator form will collect contact information for three individuals who can be contacted if a participant is unable to be reached by study staff for follow-up visits. Other baseline measures (see Table) will include the Alcohol Use Disorders Identification Test (AUDIT) [55], Self-Report of the Effects of Alcohol Questionnaire (SRE) [56, 57], Fagerström Test of Nicotine Dependence (FTND) [58], and the Nicotine Dependence Syndrome Scale (NDSS) [59], Barratt Impulsivity Scale (BIS-11) [60], UPPS Impulsive Behavior Scale (UPPS) [61], Impaired Control Scale (ICS) [62], Center for Epidemiological Studies Depression Scale (CES-D) [63], Toronto Alexithymia Scale (TAS-20) [64], the Reward Probability Index (RPI) and the Environmental Reward Observation Scale (EROS) [65]. Baseline measures that will be repeated

at subsequent visits will include the Timeline Followback (TLFB), the Penn Alcohol Craving Scale (PACS) and Tiffany Questionnaire of Smoking Urges (TQSU) [66], and the Wisconsin Smoking Withdrawal Scale (WSWS) [67]. To assess potential medication effects on changes in motivation and self-efficacy for resisting alcohol/cigarettes, we will use alcohol and smoking Contemplation Ladder items, Alcohol and Cigarette Abstinence Self-Efficacy (AASE/CASE) (these scales will be repeated at each visit) and the Inventory of Drinking Situations (IDS) scales [68-70]. Appetite and eating behavior will be assessed with the Simplified Nutritional Appetite Questionnaire (SNAQ) [71], Control of Eating Questionnaire (CEQ) [72], the Three Factor Eating Questionnaire (TFEQ) [73] and the Reward-Based Eating Drive Scale (R-BEDS) [74]. During the medication phases, side effects will be assessed with the SAFTEE questionnaire [75], a standard tool for alcohol clinical trials. Participants will also complete previously validated Purchase Tasks for alcohol, cigarettes, and food, and delay discounting will be assessed with the Monetary Choice Questionnaire (MCQ) [76-79]. These brief behavioral economic tasks assess perceived value of reinforcers by presenting hypothetical scenarios involving choices between the reinforcer (alcohol, cigarette, food) and monetary rewards; these measures will be completed at each visit. Finally a previously validated sweet taste preference test will be administered at baseline and again on the final visit, since this phenotype has been shown to be implicated in both food and alcohol reward, and may be modulated by a GLP-1 agonist. This test involves participants tasting solutions of sugar water prepared to reach .05, .1, .2, .42, and .83 molar sucrose blinded in pseudo-random order, and then rating preference and intensity of the taste. The sweet taste test will be overseen by a research assistant using previously published protocols from prior projects at UNC [80, **Error! Hyperlink reference not valid.**].

The baseline questionnaires and interview assessments are projected to take approximately 3-4 hours combined. To accommodate potential scheduling/time constraints or delays at the baseline visit, some questionnaires that are not time-sensitive (for instance, personality questionnaires) may be deferred until a later lab visit as needed, at the discretion of the study team. All interview records and paper questionnaires will be stored in study binders in a secure location for subsequent entry into an electronic database for analysis. Patients will be given breaks as needed. Following the blood draw, participants will be offered a snack and bottled water (given the instructions to arrive fasting). If results of the baseline screening/medical assessment indicate that the participant is tentatively eligible, they will be given a comprehensive orientation to the next phases of study, including the follow-up medication visits, the laboratory alcohol administration visits, and the daily surveys. Locator/collateral contact information will also be obtained. A Locator form will collect contact information for three individuals who can be contacted if a participant is unable to be reached by study staff for follow-up visits. Following the completed baseline assessments, the participant's screening summary will be reviewed for eligibility, including review of medical criteria and any medications that the participant is taking by the study physician. Lab results will be uploaded to the EMR and reviewed by the study physician prior to prescribing the medication. Potential interactions with semaglutide will be verified using an established online database such as Epocrates or Lexicomp. In the event of any uncertainties about medication interactions, participants will be asked to contact their primary care physician to confirm no concerns with taking semaglutide.

For eligible participants, the study physician will provide sign-off on all medical criteria (e.g., medical history, medications, lab results), and the PI will provide sign-off on other baseline criteria. Once participants have been confirmed as eligible, the physician will submit an order to

start medication or placebo. Medication and placebo will be dispensed at CTRC (Week 1 visit) at a date coordinated with the participant. Participants will be advised to be vigilant for symptoms of hypoglycemia at the medical visit, and instructed to contact the study team to review any symptoms that emerge (regular glucose tests will also be obtained at follow-up visits, as noted in the schedule of assessments). If necessary, the medication review will take place via telephone or telemedicine, depending on medical team availability.

Participants' Week 1 visit will be scheduled with enough lead time to review lab results and exclude participants (if needed) prior to administering the study medication. Additionally, if clarification of medical criteria is needed at any point during or following the phone or in-person screening process, or at any subsequent stage of the study, the study physician may meet with the participant via a remote contact method (e.g., phone, Webex/Zoom, or telehealth) to clarify medical questions or discuss test results.

c) Daily Assessments.

Throughout the study, participants will be asked to complete a brief self-report survey each day that includes measures of 1) prior-day number of cigarettes smoked; 2) number of drinks consumed on the prior day; and 3) prior day peak craving for alcohol and cigarettes. Participants will be provided with a paper booklet in which to enter responses and will be asked to bring the booklet to each visit. At each visit the research staff will collect the interim daily surveys for retention in the participant's study binder. Participants will be texted an automated text message each day during their participation in the study as a reminder to complete the daily survey. If preferred, participants can opt to receive an email link. (No daily survey data will be collected from participants via text or email.) At each study visit, a staff member will provide compensation for the prior week's surveys, and will review survey adherence and progress towards compensation for good adherence (described later), as a means of motivating adherence to self-report assessments. In the event a participant completes the daily assessments but forgets to bring the packet to a given visit, they will be asked to bring their packet to the following session. Participants will be asked to either a) complete the measures in person at the current lab visit, or b) to schedule a brief meeting with a research team member via Zoom or Webex in order to complete the questions (depending on scheduling and availability). These approaches will be used in specific circumstances if needed (e.g., if the participants forgets to complete the daily assessments altogether, or will be unable to bring it to the next session).

d) Weekly Laboratory Visits.

Medication administration visits will occur at either the Eastowne Clinical Research Unit (CRU) or the CTRC. Following the baseline (Week 0) visit, participants will visit CRU or UNC Hospital/CTRC once weekly (Weeks 1-9), for subsequent medication or placebo doses, and for a final follow-up/discharge visit at Week 10. (In addition, the study physician may request an additional follow-up lab visit(s) at any point in the study to monitor side effects.) In addition, to accommodate events such as missed lab visits or scheduling difficulties, assessment procedures at a given weekly visit (e.g., questionnaires, lab tests, smoking sessions) may be conducted within a 7-day window of the original target date, as necessary, to avoid unnecessary missing data. In addition to medication/placebo administration, follow-up visits will include 1) vitals, weight measurements, and a brief side-effects assessment, 2) a finger-stick glucose test (or fasting blood draw depending on the

week, see study flow chart), 3) a brief calendar-based self-report assessment of interim alcohol and cigarette use (TLFB), and 4) a repeat CO measurement. These procedures are expected to take roughly 30-60 minutes in total, and will be conducted by a trained study team member and/or a member of the CRU/CTRC team (e.g., RN). All side effects reports, labs, and other medical test results (e.g., glucose tests) will be uploaded in Epic (e.g., lab tests) or sent electronically (e.g., self-reported medication changes) for review by the study physician. If side effects or lab results suggest that further assessment is indicated, a member of the medical team will advise the study team (and if necessary, contact the participant) to provide direction. At the Week 4, Week 8, and final discharge visits, participants will be asked to arrive fasting to allow for a blood draw for follow-up lab assays (identical to those described in the baseline procedures above). As with the baseline sample, a portion of each sample will be stored for follow-up analyses (e.g., nicotine metabolites).

e) Smoking Sessions.

All participants will complete laboratory smoking lapse and self-administration sessions at dates corresponding with the baseline visit (i.e., between Weeks 0-1) and the end of the .5 mg medication phase (e.g., between Weeks 8-9). Sessions will occur during the 0.5mg dose given that some participants in the event some participants do not research the maximum 1.0mg dose. During lab sessions, participants will report to the lab at approximately 9:00am after receiving instructions to abstain from cigarettes (for 12 hours) and alcohol (24 hours). Upon arrival, overnight abstinence will be verified based on expired CO of <6ppm (or <50% of the initial screening reading). Upon arrival participants will complete measurements of body weight and vitals (HR, BP). Participants will also provide a finger-prick blood glucose test for an instant reading on a blood glucose monitor.

Simulated lapse. The simulated smoking lapse procedure was developed by McKee, who is a consultant on this project [23, 52]. The McKee paradigm is the only validated laboratory procedure that models smoking reinstatement and self-administration in the same procedure [23]. In this procedure, a nicotine deprivation period (e.g., overnight abstinence) provides a context to study medication effects on reinstatement [23]. Given the requirement of overnight abstinence prior to the lapse session, it is important to maximize the likelihood of the participant adhering to these instructions. Failure to maintain overnight abstinence could result in having to reschedule the session. Therefore, participants will be offered a bonus of \$25 for completing the overnight abstinence requirement, as additional incentive to adhere to the abstinence instructions. Sessions will be conducted in a laboratory space equipped with a fume hood; participants will be seated near the hood and will be instructed to direct exhaled smoke into the hood. Research staff will be required to don protective equipment (e.g., N95 mask and face shield) when present in the room during the time of the task, and will remain outside the room during the procedure, to the extent possible.

Upon beginning the task, participants will be presented with a package of their preferred cigarettes (participants will be asked to bring one unopened pack in to the session). Participants will be given the choice to initiate cigarette smoking, or to delay smoking for up to 50 minutes in exchange for monetary reinforcement. Prior studies show that a reinforcement schedule of \$1 for every 5 minutes results in participants resisting, on average, for 25 minutes, providing ideal variability in time to reinstatement [23]. If no lapse occurs (i.e., the participant resists for 50 minutes), participants will not be forced to smoke a cigarette. Following the initial decision to smoke, participants will complete assessments of craving, withdrawal, and subjective effects (described below).

Next, a 60-minute period of ad libitum smoking will ensue [53]. Participants will be presented with a tray containing 8 cigarettes from the package, and will have the opportunity to smoke additional cigarettes at their discretion [53]. Again, participants will not be forced to smoke a cigarette. Repeated ratings of craving, withdrawal, and subjective effects will be taken at 15-minute intervals during the self-administration period. A follow-up measure of expired CO will be taken at the end of the session to measure CO “boost”, an additional index of cigarette intake.

The primary outcomes for the human laboratory sessions consist of 1) nicotine reinstatement (i.e., minutes of resistance to smoking reinstatement), and 2) nicotine self-administration (i.e., cigarettes consumed during ad libitum smoking). These primary outcomes are selected because they reflect objectively defined behaviors analogous to those reported in preclinical studies. Secondary human laboratory outcomes will include CO boost and subjective effects during nicotine self-administration, e.g., assessed by the Modified Cigarette Evaluation Scale [54] and the Drug Effects Questionnaire [55]. The Profile of Mood States Short Form (POMS-SF) will also assess change in mood.

Cue-elicited craving. Human studies of the effects of GLP-1 receptor agonists on cue-elicited drug craving have not been reported. As an exploratory aim, we will also utilize an established cue reactivity task to assess peak provoked craving (PPC). This procedure, which involves assessing craving during a cue exposure task (lighting a cigarette and attending to cues) while in a period of short-term abstinence, has been demonstrated to reliably induce acute craving [57]. Given the potential for differential medication effects on tonic vs. phasic craving [58], tonic craving will also be assessed as a component of the repeated self-report assessments (noted below). The PPC task will be administered at week 8, +/- 7 days.

List of Study Assessment Measures (See Section 1.3 for assessment time points)

1. Demographics form
2. Timeline Follow-Back (TLFB)
3. Structured Clinical Interview for DSM-5 Mental Disorders (select modules)
4. MINI Neuropsychiatric Interview (select modules)
5. Sweet Taste Preference Test
6. Alcohol Use Disorder Identification Test (AUDIT)
7. Self-Report of the Effects of Alcohol Questionnaire (SRE)
8. Center for Epidemiological Studies Depression Scale (CES-D)
9. Toronto Alexithymia Scale (TAS-20)
10. Barratt Impulsivity Scale (BIS-11)
11. UPPS Impulsive Behavior Scale (UPPS)
12. Reward Probability Index – Environmental Reward Observation Scale (RPI-EROS)
13. Impaired Control Scale (ICS)
14. Fagerstrom Test for Nicotine Dependence (FTND)
15. Nicotine Dependence Syndrome Scale (NDSS)
16. Penn Alcohol Craving Scale (PACS)
17. Tiffany Questionnaire of Smoking Urges (TQSU)
18. Wisconsin Smoking Withdrawal Scale (WSWS)
19. Wisconsin Inventory of Smoking Dependence Motives (WISDM)
20. Alcohol and Smoking Contemplation Ladder
21. Three Factor Eating Questionnaire (TFEQ)
22. Reward-Based Eating Drive Scale (R-BEDS)

23. Control of Eating Questionnaire (CEQ)
24. Simplified Nutritional Appetite Questionnaire (SNAQ)
25. Monetary Choice Questionnaire (MCQ)
26. Cigarette Abstinence Self-Efficacy (CASE)
27. Alcohol Abstinence Self-Efficacy (AASE)
28. Inventory of Drinking Situations (IDS)
29. Cigarette Evaluation Questionnaire (CEQ)
30. Drug Effects Questionnaire (DEQ)
31. Alcohol Purchase Task (APT)
32. Cigarette Purchase Task (CPT)
33. Food Purchase Task (FPT)
34. Profile of Mood States – Short Form (POMS-SF)
35. Peak Provoked Craving (PPC)
36. Systematic Assessment for Treatment Emergent Effects (SAFTEE)
37. Obsessive Compulsive Drinking Scale
38. Graded Pain Scale

Analysis schedule. Analyses of side effect frequency and AE/SAE frequency will be conducted prior to scheduled DSMB meetings. Other analyses will be conducted following the completion of the trial, or as otherwise required to fulfill DSMB requests or other reporting requirements.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This Phase II trial is intended to produce initial data on the effects of semaglutide in dependent smokers, with an emphasis on human laboratory outcomes. The dose escalation schedule is based on the standard clinical regimen, which is intended to minimize side effects common to GLP-1 agonists (i.e., nausea). Participants in the placebo group will complete an identical sequence while receiving sham subcutaneous injections (a small needle stick using a micro-needle of the same size, without an injection). This placebo condition is selected due to the absence of an available matching placebo cartridge from the manufacturer (see section 4.3). All participants will complete laboratory smoking lapse sessions at two time points, corresponding with the baseline and 0.5mg, phases. This design allows for within-subjects analyses for laboratory outcomes that are best examined at the within-subject level (owing to high inter-individual variability in nicotine pharmacokinetics).

4.3 JUSTIFICATION FOR DOSE

Semaglutide (Ozempic®) will be administered according to the FDA-approved dose escalation schedule, which begins with a starting dose of 0.25mg (for titration purposes) once per week for four weeks. At week five, dosage is increased to 0.5mg/week (the initial first maintenance dose) for a subsequent four weeks, at which point dosage can be increased further (1.0mg) if indicated (and presuming that the 0.5mg dose has been tolerated). The intent for this initial trial is to mimic the typical clinical scenario over the first several weeks of medication titration, concluding with one dose of the maximum Ozempic® dosage (1mg). Although the newer semaglutide pens (Wegovy®, approved in June 2021) deliver semaglutide at dosages up to 2.4mg, we will not exceed 1mg for this initial study. Although primary analyses will focus on the 0.5mg dosage, participants will receive one week of 1.0mg treatment

at the conclusion of the 0.5mg phase, in order to collect initial data on side effects and naturalistic drinking/cigarette use at this dosage in the current population. Participants will be monitored carefully and will not be escalated to the next dose if experiencing persistent side effects indicative of poor tolerability.

Given the lack of a true placebo (i.e., no manufacturer-developed placebo Ozempic® pens/cartridges) for study, we will use a placebo condition that consists of weekly sham doses. Sham doses will involve a brief needle prick using a very small (e.g., 32 gauge) needle, using either the NovoFine proprietary needle (as is used in the Ozempic® and Wegovy® pens) or a micro-needle of a similar gauge (e.g., an insulin needle). These procedures are described in more detail later in this protocol. By necessity, medical staff administering the medication at the CRU or CTSC cannot be blind to condition. However, other experimenters and outcomes assessors will remain blind to condition. Participants will be instructed during the informed consent and study orientation that they have a 50/50 chance of being randomized to medication and placebo groups.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last study visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last study visit or procedure shown in the SoA in the trial overall.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet the following criteria:

- Age 21-65
- Smoking 5+ cigarettes per day (on average) over the past year, with no period of abstinence > 90 days
- Biochemical verification of smoking status, based on expired CO \geq 8 at baseline
- Willingness to take study medication and complete study procedures
- Willingness to complete lab sessions involving cigarette smoking
- Ability to communicate in English

5.2 EXCLUSION CRITERIA

- Regular use of electronic nicotine delivery systems (ENDS/vaping), cigars, chewing tobacco or snuff, based on at least weekly use in the past 30 days
- Past 30-day use of nicotine replacement therapies/products
- Reporting past 30-day use of illicit drugs other than cannabis at baseline, or having a positive toxicology screen for illicit drugs other than cannabis at baseline

- Current engagement in alcohol or smoking cessation treatments, or currently engaged in intentional efforts to quit alcohol use
- Past 30-day use of: Sincalide, Sulfonylureas, insulin and insulin products or other medications that may interact with semaglutide, or weight control medications
- Prior use of semaglutide or other GLP-1 agonists
- Known or suspected hypersensitivity to study medication or related products
- Lifetime diagnosis of severe mental illness (including schizophrenia and bipolar disorder)
- Meeting criteria for current alcohol use disorder (AUD) or other substance use disorder (with the exception of tobacco or mild cannabis use disorder)
- History of suicide attempt, or recent (past 30 day) suicidal ideation, or psychiatric hospitalization in the last 6 months
- Current significant medical or neurological illness (based on self-report or medical record) including severe hepatic impairment or cirrhosis, impaired renal function (eGFR <50ml/min), acute or chronic pancreatitis, gastroparesis, gallbladder disease or cholelithiasis, other severe gastrointestinal disease, heart failure, coronary artery disease, stroke, seizure disorder, or other medical condition that poses a risk for the medication or alcohol administration components of the study (as determined by the MD)
- A personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B
- Calcitonin greater than or equal to 50 ng/L
- Uncontrolled thyroid disease at screening
- History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g., subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery)
- History of Type 1 or Type 2 diabetes, or HbA1c >6.5% measured at screening
- History of diabetic retinopathy, proliferative retinopathy, or maculopathy
- History of diabetic ketoacidosis
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and carcinoma in situ)
- Currently nursing, pregnant, anticipating pregnancy in the next 6 months, or not using a highly effective contraceptive method as judged by the MD, and defined as:
 - a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
 - b. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
 - c. intrauterine device
 - d. intrauterine hormone-releasing system
 - e. bilateral tubal occlusion
 - f. vasectomized partner
 - g. sexual abstinence
- Elevation of serum lipase, amylase, direct (conjugated) bilirubin, or alkaline phosphatase (ALP), ALT, or AST) more than 3X the upper limit of normal on baseline bloodwork

- Baseline body mass index (BMI) <23kg/m²
- Uncontrolled hypertension or systolic BP >180 mmHg and/or diastolic BP >105 mmHg, averaged from three measurements
- Plans for travel outside of the local area in the upcoming 12 weeks that would interfere with lab visits during the study period (or other logistic factors that would make it difficult to commit to entire duration of study)

5.3 LIFESTYLE CONSIDERATIONS

Specific lifestyle instructions will include:

- Refrain from alcohol consumption or other drug use for 24 hours prior to smoking sessions
- Refrain from smoking for 12 hours prior to arrival at smoking sessions
- Arrive fasting at sessions scheduled for blood draws as needed (e.g., Weeks 0, 4, 8, and final discharge visit)
- Women participating in the study must report being willing to use a reliable birth control method during the trial (if sexually active), and must report no plans for pregnancy in the next 6 months.
- Participants will also understand that they may be excluded if they test positive for drugs other than cannabis during the time of scheduled drug screens (repeat drug tests will take place during weeks 4 and 8).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Examples of screen failures would include participants excluded following baseline laboratory work, or those excluded based on a change in treatment-seeking status at the time of the baseline assessment. Individuals who do not meet the criteria for participation in this trial (screen failure) because of a specific modifiable factor (e.g., upcoming travel) may be rescreened at a later date. Rescreened participants will be assigned the same participant number as for the initial screening. Data pertaining to screening failures will be tabulated in an anonymized fashion.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited from the community through advertisements, which may include ads in local online or print newspapers, bus advertisements, print flyers placed in community or hospital settings, business cards, campus listservs, and online postings (e.g. Craigslist (ads will not be placed in employment section)), and social media ads (Facebook, Twitter, Instagram) that direct potential participants toward a study website/landing page (hosted on Research for Me). Participants may also be

recruited from local medical clinics (e.g., primary care clinics) that grant approval for assisting with recruitment (e.g., by placing study advertisements in clinics). Flyers and online advertisements will include study contact information and a web link and/or QR code leading to the landing page.

In addition to these “passive” methods of recruitment, we will also include “active” recruitment methods. These methods will include members of the study team setting up recruitment booths and passing out business cards at public events (e.g., festivals) or public venues. Once initial contact with participants is made (e.g., via email or in person), research staff will schedule the participant for a phone call to explain the study and conduct a screening interview.

Participants will receive compensation. The payments will be allocated as follows (please see 1.2 for a summary of all scheduled sessions):

- \$50 for completing the consent/screening/baseline sequence (Week 0)
- \$100 for smoking session 1 (To be scheduled between Weeks 0-1)
 - Includes \$75 for attendance, plus a \$25 payment after confirming overnight abstinence.
- \$100 for smoking session 2 (To be scheduled between Weeks 8-9)
 - Includes \$75 for attendance, plus a \$25 payment after confirming overnight abstinence.
- \$30 per visit for each follow-up/medication administration visit during Weeks 1-10 (10 visits x \$30 per visit = \$300)
- Up to \$150 for completing and returning daily questionnaires over the study period (\$15 per weekly set of surveys x 10 weekly visits), which includes the week following the 1.0mg dose, to be paid at weekly medication visits)
- A \$50 bonus for completing at least 9 of 10 weekly assessments
- Participants will receive a final bonus of \$100 for completing the study through Week 10 (to be paid at the final discharge visit).

Therefore, the total maximum compensation over 10 weeks for study visits is \$850. Compensation for smoking sessions will occur at the end of each session. The final payment (including bonuses) will be paid at the Week 10 discharge visit. Overall, these payments are structured to maximize retention in the study (given the long dose escalation period and time-intensive laboratory sessions). Additionally, an incentive-based structure that includes weekly incentives is important to reinforce engagement with daily surveys and minimize missing data. Participants will be updated at each visit with their progress toward the bonus incentives for adherence (e.g., weekly bonus of \$10 and progress toward final adherence bonuses). In the event participants are not able to pick their final payments in person, we will offer the option of issuing the final payment via electronic gift card to the participant’s email address, with their permission.

We anticipate phone screening up to 400 individuals and randomizing up to 48 participants to medication or placebo conditions, in order to obtain a final sample of 36 eligible participants who complete the full course of the 0.5mg phase (allowing for 25% attrition). If attrition is higher than anticipated, we will attempt to enroll additional participants to arrive at a final sample of 36 participants who complete study procedures through the end of the 0.5mg dosage phase (i.e., through the end of Week 9).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Semaglutide is a relatively new (approved as Ozempic® in 2017) GLP-1 receptor agonist. A new oral formulation of semaglutide was approved by the FDA in 2019, making semaglutide the first drug in its class to be available in both subcutaneous and oral formulations. Most recently, semaglutide was approved in a higher-dose formulation for the treatment of overweight/obesity (Wegovy®, June 2021). GLP-1 agonist medications were designed to mimic the function of the endogenous GLP-1 peptide, with the benefit of a much longer half-life than endogenous GLP-1. Based on their glucose-lowering and appetite-reducing properties, GLP-1 agonists were developed as anti-diabetic therapies. Several GLP-1 agonists (e.g., exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide,) are now in widespread use as treatments for type II diabetes (T2D); these medications have also proven efficacious for weight loss, reducing glycated hemoglobin (HbA1c), and reducing risk for some cardiovascular events [29]. Although the primary indication of GLP-1 agonists is T2D, these therapies are increasingly being studied for other indications in non-diabetic patients, including obesity/weight management. In June 2021, the FDA approved semaglutide at a higher dosage (2.4mg/week) for the indication of weight management, under the brand name Wegovy®.

6.1.2 DOSING AND ADMINISTRATION

Semaglutide (Ozempic) will be administered according to the FDA-approved schedule, which begins with a starting dose of 0.25mg once per week for four weeks. At week five, dosage is increased to 0.5mg for a subsequent four weeks (initial maintenance dose), after which point dosage can be increased further (to 1.0mg), presuming the medication is well tolerated.

Although semaglutide can be self-administered in the home setting, medication and placebo administration will be delivered by a research nurse or other medical team member at Eastowne CRU or CTRC in order to execute the placebo manipulation and ensure adherence to medication. This approach also allows us to collect safety outcomes on a regular basis, further ensuring that participants will be monitored carefully. Semaglutide is administered subcutaneously (in the abdomen, thigh, or upper arm). Doses are delivered via the Ozempic® pen, a cartridge-based device that calibrates medication delivery based on the desired dose. An extremely small needle (4mm, 32-gauge needle – the size of 2 human hairs) is used to deposit the medication subcutaneously. Participants in the medication group will receive weekly semaglutide injections at 0.25mg/week for 4 weeks, followed by 0.5mg/week for 4 weeks), followed by 1 week at 1.0mg. This schedule results in 9 medication administration sessions. At the week 9 visit, the 1.0mg dose will be delivered as 2 x 0.5 mg doses given in succession. This is because the medication pens being used for this study deliver dosages of 0.25 and 0.5mg, and participants are not being maintained on the 1.0mg dose after week 9. This timeframe also allows sufficient time to reach steady-state plasma concentration levels (achieved within 4-5 weeks of initiating the starting dose).

At the present time, we do not have access to a manufacturer-developed placebo (the medication relies on the proprietary Ozempic® pens for delivery). Therefore, this study will use weekly sham injections for the placebo group. Sham doses will involve a brief needle prick using a very small (e.g., 32 gauge) needle, identical to the one used in the Ozempic® pens (NovoFine), or a needle of similar gauge (e.g., an insulin needle). During medication and placebo administration, participants' view will be shielded from the injection site to prevent unblinding. Medication will be delivered in the upper arm, abdomen, or thigh. Given the extremely small volume of the injections, we will not utilize saline or another inert substance for the placebo administration; rather, the sham doses will consist of briefly inserting the micro-needle.

Due to the nature of the placebo condition, it will not be possible to blind the staff RNs administering the medication. However, we will provide training to study staff to minimize the likelihood of contaminating the blinding procedures. We will also develop procedures to minimize contact between the RNs and outcome assessors. All other staff members (including research assistants and outcomes assessors) will remain blind to condition, unless unblinding is necessary (e.g., due to an adverse event).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The team will collaborate with IDS to source the medication (and NovoFine or insulin needles for the placebo condition), which will be sourced and stored at the IDS pharmacy prior to dispensing. Participants assigned to medication will be prescribed one Ozempic® pen following randomization. As per IDS requirements, in between study visits participants will be given their assigned medication pen and asked to bring their pen back to each follow-up visit. In between visits, pens will be placed in a small plastic container and then encased opaque, tamper-proof bag in order to prevent unblinding. (For participants in the placebo condition, a plastic object of roughly equal size and weight will be placed in the plastic container and medication bag.) Participants will be instructed not to open the bag in between visits. A refill pen will be prescribed prior to the Week 7 visit, once the doses from the first pen have been allocated. Any unused doses from individual pens (e.g., in the event of participant drop-out) will be discarded/destroyed by IDS, as will any pens that expire during the course of the trial. In the event a pen expires before a participant completes the study, a replacement pen will be prescribed at the discretion of the study physicians.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Ozempic® is manufactured by Novo Nordisk. As described above, the medication is dispensed from a proprietary device, the Ozempic® pen. Each pen contains 2mg of medication, requiring that each participant is prescribed two pens over the course of the study. A full description and visuals can be found at the following site:

<https://www.Ozempic®pro.com/how-to-prescribe/Ozempic®-pen.html>

The *placebo group* will receive sham injections that involve a brief needle-prick without dispensing a substance. The needles used for the sham injections will be the NovoFine 32G needle, the same needle in the Ozempic® pen (<https://www.novoneedles.com/novofine.html>) or a comparable needle of a similar gauge (e.g., an insulin needle). In no case will any fluid be injected during placebo sessions. To mimic the active medication administration, the medical staff member will insert the microneedle briefly and then remove it while the participant's view is shielded.

6.2.3 PRODUCT STORAGE AND STABILITY

Pens will be dispensed from IDS. For drug dispensing visits at CRU (Eastowne), scheduled for Weeks 1 and 7, pens will be delivered the day of the visit by courier. Ozempic pens will be kept in the participant's possession (sealed in a tamper-proof bag) between visits. According to the manufacturer, following the first use, the Ozempic® pen can be stored for up to 56 days at room temperature (59 to 86 F) or refrigerated at 36 to 46 F. As per our plan developed in collaboration with IDS, participants will be

instructed to keep the medication bag at room temperature for simplicity. Each participant's pen will be labeled with the study ID number and pens will not be shared across participants. Placebo needles will remain packaged until use, and will be stored at room temperature in a secure location.

6.2.4 PREPARATION

Semaglutide does not require advance preparation; cartridges are pre-filled and doses are calibrated using the pen device. The RN or medical staff member will select the correct dosage and administer the medication as per manufacturer guidelines.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Following the baseline assessment, participants will be randomized to medication or placebo conditions at a 1:1 ratio by a member of the IDS team using a pre-determined randomization scheme. Medication and placebo administration will be carried out by a staff RN at CRU or CTTC. Due to the nature of the placebo condition, it will not be possible to blind the RNs to condition. However, all other staff members will remain blind to condition, and the staff members administering medication will be trained in protecting the blind (e.g., redirecting the conversation if the participant comments about medication condition; minimizing contact with experimenters.) To maintain blinding of participants, participants' view will be shielded and they will be asked to face away from the injection site during all placebo and medication administrations. Aside from the staff members administering medication, no study team members interacting with participants will be aware of participants' assignments. At the stage of interim analyses (e.g., in preparing safety reports for DSMB meetings) and final analyses, the study statistician will be provided with the assignment log. None of the study personnel involved in recruitment or enrollment will have knowledge of the details of the randomization table that will be used by the IDS pharmacy.

At the completion of the trial, participants will be provided with a questionnaire asking about perceived medication assignment (to assess the success of maintaining the blind). Due to common side effects of semaglutide (in particular nausea), we do not expect blinding to be successful in all cases.

6.4 STUDY INTERVENTION COMPLIANCE

Medication will be administered by CRU or CTTC staff to assure compliance and reduce potential sources of non-adherence. A missed session will constitute a missed medication dose. As per manufacturer directions, any missed doses/appointments will be corrected by asking the participant to come in for the dose as soon as possible within 5 days of the missed dose. After the 5-day mark has passed, the dose will be skipped and the participant will resume with the next scheduled dose. Study medication logs will serve as the primary source document for tracking medication and placebo administration. Participants will be coded as non-adherent if they miss more than 2 scheduled doses between Weeks 1-9. In the event of missed medication doses or missed appointments, the physician will have the discretion to adjust the appointment date (within the manufacturer or standard practice guidelines), or to prescribe a replacement pen if needed to accommodate the target medication schedule.

6.5 CONCOMITANT THERAPY

Participants may be taking medications for other conditions (provided those treatments are not included in the list of exclusion criteria). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Changes to medication status or other treatments will be assessed at each in-person visit, with any changes reviewed by a study physician. Should a concomitant therapy preclude further participation for safety or scientific reasons (for instance, if a participant starts a therapy that constitutes an exclusion factor), this issue will be discussed by the study leads and the participant will be excused from further participation, if required to ensure safety. By definition, participants will not be seeking treatment for smoking cessation. If a participant makes the decision to seek treatment for smoking during the study, s/he will be referred to appropriate treatment resources and excused from further participation.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Study discontinuation: The study may be halted if deemed necessary by the lead investigators, DSMB, or IRB. Examples of reasons for study discontinuation include unexpectedly high frequency of serious adverse events, or significant increases in alcohol use during treatment, leading to the conclusion that the medication is not safe in this population. In addition to the participant discontinuation rules noted below, the following study stopping rules will trigger halting the study pending a DSMB evaluation: 1) Occurrence of any hospitalization or any SAE rated at Grade 4-5 (CTCAE) in a medication-treated participant (and deemed likely to be medication-attributable); 2) Documentation of SAEs in >3 medication-treated participants that are deemed likely attributable to medication; 3) Removal of >5 subjects due to adverse events deemed attributable to study-related procedures, inclusive of SAE and/or medical stopping rules (e.g., weight, disease progression), as defined in 7.2 below. In order to classify events as medication-attributable, the PI will request that IDS breaks the blind and provides a file containing condition assignment to the study physician(s). If any of the aforementioned events trigger a DSMB meeting, the full randomization table will be provided to a statistician, so that group differences can be fully evaluated at the meeting. Given the safety profile of semaglutide for other clinical conditions, as well as preclinical evidence that GLP-1 receptor agonists reduce drug intake, these scenarios are expected to be unlikely.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. The investigators may discontinue or withdraw a participant from the study if clinically or otherwise indicated. Examples of reasons for removing a participant include:

- Significant study intervention non-compliance
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation that indicates that continued participation in the study would be unsafe
- Pregnancy
- Diagnosis of significant disease or disease progression which requires discontinuation of the study intervention
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant relocates from the local area, or is otherwise unable to attend visits
- Significant or persistent side effects that pose significant discomfort or preclude escalation to the 0.5mg dose (e.g., persistent and severe nausea, or hypoglycemia, as indicated by repeated fasting glucose values below normal 54 mg/dL
- Changes in lab tests or clinical status from baseline that render the participant ineligible to continue in the judgement of the physician(s) (e.g., elevated liver enzymes, elevated serum amylase or lipase levels, weight loss as defined below)
- Excessive weight loss (defined as loss exceeding 5% of baseline weight or BMI < 20)
- A change in treatment-seeking status (i.e., the participant expresses a desire to enter treatment for smoking cessation).
- Any other change in medical status or side effects that is significant enough to warrant removal in the judgement of the study physicians.

If a participant exhibits changes in symptoms or clinical status that warrant potential removal, the study physicians will confer and render a decision as to whether to withdraw the participant. With respect to dosage increase, if a participant's side effects profile or laboratory tests during the initial 4-week phase (.25mg) indicate that s/he is unable to safely proceed to the 0.5mg dose, the participant may be removed from the study at the discretion of the physicians. If lab tests or side effects during the standard maintenance dose of 0.5mg suggest that a participant is unlikely to tolerate a higher dose (1mg), they may be excluded from the 1.0mg dose escalation at the discretion of the physicians. In this case, participants will be given the option of one additional week at the standard therapeutic dose of 0.5mg (i.e., highest tolerated dose). Reasons for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention (e.g., fail to attend the Week 1 visit for randomization) may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, may be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled medication visits and is unable to confirm attendance at the following visit (or is unable to be contacted by the study staff).

The following actions will be taken if a participant fails to return to a required study visit:

- The team will attempt to contact the participant and reschedule the missed visit within one week, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- The team will attempt to contact the individuals that the participant had listed on the Locator Form at baseline (maximum of three attempted contacts per individual).
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, up to 3 telephone messages, up to 3 email messages, and if necessary, a letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The efficacy assessments/outcomes are noted in summary form in section 3. The ascertainment of these outcomes is described in further detail in section 4 (study design). Briefly, the efficacy endpoints are human laboratory measures of nicotine reinstatement and cigarette smoking, self-reported cigarette consumption over the course of the trial, subjective responses to smoking in the laboratory, and changes in body weight.

8.2 SAFETY AND OTHER ASSESSMENTS

Safety and assessments are summarized in detail in the study design section (Section 4.1). Briefly, safety assessments include a baseline assessment, body weight, bloodwork, vitals signs, and clinical interview to assess substance use and psychiatric symptoms. Follow-up medical visits will include repeat assessments of bloodwork and scheduled time points, as well as follow-up measurements of body weight and vitals signs. Medication side effects will be assessed at each visit, and a study team member will contact participants within 2-3 days of each dosage increase to evaluate potential side effects. Other assessments (questionnaires, interviews) are noted in Section 4.1.

If an urgent medical situation arises at either medication or smoking visits, a team member will contact the physicians on the team to consult, based on a predetermined sequence (e.g., contact physician A, followed by physician B, then physician C). Additionally, any participants who express a desire to seek treatment during the study will be excused from further participation and provided with smoking cessation resources. Co-I Dr. Jordan directs outpatient addiction treatment at UNC-CH.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include an adverse reaction requiring intensive treatment in an emergency room or at home.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The study physicians will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. At weekly medication visits, all participants will review a side effects checklist (SAFTEE) with a research assistant, which will then be provided for review by a medical staff member at CTRC. The staff member will begin with an open-ended question about side effects or any other adverse events, followed by a review of specific side effects using the SAFTEE. Any previously reported side effects will be queried to determine any change in status (presence or severity). These weekly visits will be a primary method for identifying side effects. Additionally, a research staff member will contact participants by phone in the week following the initial dose, as well as the week following each dose escalation. Phone calls will be scheduled 2-3 days following these events.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Under the direction of the PI, members of the research team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Any such events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All project staff will be trained to identify adverse events (AEs), which must be reported to the PI and study physicians within 24 hours. In addition, any unanticipated participant issues will be discussed in weekly staff meetings, which will provide another opportunity to identify AEs.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Research staff will be trained to report potential AEs or SAEs to the PI immediately. For any potential AEs/SAEs, the study physician will make a determination to distinguish between AEs, SAEs and unanticipated problems and provide judgment about attributions. Management and reporting of AEs, SAEs, and unanticipated problems will be carried out in accordance with Good Clinical Practice (GCP) standards, as outlined by the Food and Drug Administration. AEs will be defined as any negative medical

event during the trial (whether or not the event is deemed related to the study medication). SAEs are defined as events that are potentially life threatening or result in death; cause congenital malformation; result in persistent/significant disability or incapacity; require inpatient hospitalization or prolongation of hospitalization; or reflect an otherwise notable medical event in the judgment of the study physician. AEs/SAEs will be monitored regularly by the study research team and medical staff, in particular by inquiring about adverse events at each weekly visit. Should AEs or SAEs occur, they will be recorded, rated as mild/moderate/severe by the study physician, and reported in accordance with UNC IRB requirements and GCP standards. Any AEs will be reported to the IRB in progress reports and at the conclusion of the study. SAEs and unanticipated events will be reported to the IRB and DSMB within 48 hours, and to NIDA if judged as treatment-related. All staff working on this study will be made aware of the monitoring and reporting requirements for AEs/SAEs, and will have completed GCP training and other trainings required to conduct human subjects research at UNC.

Any AEs, SAEs or unanticipated problems will be followed until resolution by the PIs and/or research staff. Participants will be contacted regularly during follow-up and any observations of AEs/SAEs will be discussed among the PIs and the study physician at regular meetings (or immediately, in the event of SAEs or unanticipated problems). In the event of SAEs or unanticipated problems, the physician and study PIs will be notified immediately, and the participant will be referred to or provided with appropriate medical support.

Participants will be advised to seek prompt medical attention in the event of an unanticipated medical event. In the event of an SAE, a member of the study medical staff will maintain regular contact with the participant until the event is resolved and fully documented. A determination of relatedness to medication will be made based on symptoms, timing, and other factors.

Monitoring will be the primary responsibility of the PI. In addition, a Data and Safety Monitoring Board will be established to maximize safety (the TraCS DSMB has been engaged for this project, and will review progress at their scheduled semiannual meetings during the trial).

8.3.7 REPORTING EVENTS TO PARTICIPANTS

If an event is deemed an AE or SAE, participants will receive a phone call from study personnel to inform them that the event has been recorded and will be reported as such. Any incidental findings uncovered during the baseline medical exam or weekly visits (e.g., via bloodwork or other measurements) will be reported to the participant by the study physician, and an appropriate follow-up plan will be recommended to the participant.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Women enrolled in the trial will be asked to confirm that they are able to use a reliable contraception method for the duration of the trial and for at least 2 months after receiving the final medication dose. At the baseline visit, female subjects will undergo a urine pregnancy test upon arrival to the clinical site.

In the case of a positive pregnancy test, the participant will be notified immediately, and study participation will be halted. If any follow-up plan is recommended by the study physician, the physician or PI will communicate this recommendation to the participant.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Any UPs identified by the study team will be discussed amongst the study leadership team, and corrective actions will be identified. If applicable, a protocol amendment will be developed and submitted to the IRB.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB), and if applicable, the DSMB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

In the case of a UP that may impact participants’ safety or alter their experience during the trial (e.g., by necessitating a change in protocol), participants will be notified by a study team member at the subsequent visit. In the event of any UP that may have an imminent impact on participant safety, a team member will contact the participant by phone to inform them of the problem.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
 - Nicotine reinstatement (i.e., minutes of resistance to smoking reinstatement), and nicotine self-administration (i.e., cigarettes consumed during ad libitum smoking) during laboratory smoking procedures (co-primary endpoints). The effect of interest is the interaction between medication group (semaglutide vs. placebo) and time/dosage (baseline vs. 0.5mg). The baseline session will take place between Weeks 0 and 1, and the 0.5mg session will take place between weeks 8 and 9.
- Secondary Efficacy Endpoint(s):
 - Changes in subjective responses to nicotine during laboratory smoking procedures (drug effects and mood). The effect of interest is the interaction between medication group (semaglutide vs. placebo) and time/dosage (baseline vs. 0.5mg). The baseline session will take place between Weeks 0 and 1, and the 0.5mg session will take place between weeks 8 and 9.
 - Changes in cigarette consumption over the course of the trial, as assessed via daily cell phone surveys. The effect of interest is the interaction between medication group (semaglutide vs. placebo) and time (Week 1 to Week 10).

All primary analyses are superiority analyses. Additional details are provided in 9.4.2.

9.2 SAMPLE SIZE DETERMINATION

Because no human data on semaglutide's effects on smoking-related outcomes is available, there is no a priori effect size estimate to facilitate power calculations on these particular outcomes. We will seek a final sample size of 36 participants. Our analyses suggest that this allows sufficient power (.80) to detect a medium effect size ($f = .25$) for an interaction between group (medication vs. placebo) and dosage (baseline, 0.25mg, 0.5mg). This estimate assumes an alpha level of .05 and a within-person correlation (r) of 0.5 across time points. Further, because our mixed multilevel model (MLM) analyses will involve more time points for certain analyses (e.g., daily assessments), this approach will increase power further, which is advantageous in the event that medication effects are in the small range. Assuming a 25% attrition rate, we anticipate needing to randomize up to 48 participants to arrive at a final sample of 36.

9.3 POPULATIONS FOR ANALYSES

Primary analyses will include all participants who were randomized and received a medication or placebo dose following the week 0 visit (randomization will occur after the Week 0 visit, just prior to the Week 1 visit). MLM analyses can accommodate missing data, allowing inclusion of participants without complete data (e.g., missed visits or missed daily survey responses).

A supplementary per-protocol analyses will be conducted using all participants who received 1) at least 7 of the 9 scheduled doses, and 2) those participants who receive the final (1.0mg) dose. This planned

analysis will be conducted irrespective of the number of participants in these groups. If the sample permits, an exploratory subgroup analysis will examine participants as a function of weight (overweight/obese vs. not overweight or obese).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Primary analyses will rely on multilevel models (MLM), which are well suited to examining within-person changes over time, while also accommodating missing data and unequal group sizes, and allowing the evaluation of between-subjects moderators (e.g., overweight/obesity status) if necessary. MLM with maximum likelihood estimation can accommodate missing data under the assumption that the data are missing at random. Secondary, sensitivity analyses will be conducted to test the robustness of study findings for violations of the assumption that data is missing at random. Specifically, we will examine if baseline variables are associated with data missingness (for instance, age, sex, level of substance use) using t-tests and chi-square analyses (for continuous and dichotomous variables, respectively). Baseline variables that are associated with data missingness will be included as covariates in additional adjusted models (that adjust for the baseline variables related to missingness). Assumptions for the statistical methods being used will be tested. Should there be evidence of violations of these assumptions (e.g., presence of outlying and influential cases, distributional concerns for residuals, and so on), appropriate corrective actions will be taken. Sensitivity analyses will be used to determine the extent to which the main study results are influenced by these violations. We will focus our interpretations on small p-values ($p < .05$) that indicate evidence against the null hypothesis. We will report the number of decimal places of the p-value in line with the journal's guidelines and APA recommendations (usually 2 or 3 decimal places). For specific outcomes, the units of measurement and expected ranges of values (or example ranges, if the full range is unknown) are noted in the subsequent analysis sections 9.4.2 and 9.4.3. Any extreme outliers (defined as >3.0 standard deviations from the mean) will be recoded to one unit greater than the next most extreme value, in order to reduce undue influence of extreme outliers. For all statistical tests, confidence intervals will be evaluated in combination with tests of statistical significance. Assumptions for the statistical methods being used will be tested. Should there be evidence of violations of these assumptions (e.g., presence of outlying and influential cases, distributional concerns for residuals, and so on), appropriate corrective actions will be taken. Sensitivity analyses will be used to determine the extent to which the main study results are influenced by these violations.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Smoking sessions: MLM will be used to examine changes in nicotine reinstatement and number of cigarettes consumed (co-primary outcomes) as a function of medication phase (baseline; 0.5mg). These analyses will use medication phase as the within-subjects factor and condition (semaglutide vs. placebo) as the between-person factor.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Daily self-report data: We will use MLM to estimate within-person changes in primary outcomes (e.g., daily cigarette use over the trial period), using study week as the within-subjects factor and condition (semaglutide, placebo) as the between-person factor. A similar analysis will be applied to examine changes in body weight over the course of the trial.

Smoking sessions: MLM will also be used to examine changes in self-reported drug and mood effects during laboratory smoking as a function of medication phase (within-person) and drug condition (between person). These analyses will focus on the subjective questionnaires administered immediately after the first cigarette smoked during the 2-hour smoking lapse/self-administration session.

9.4.4 SAFETY ANALYSES

Total side effects reported (e.g., 0-15), and number of severe side effects reported during each medication phase will be assessed using MLM with medication phase (baseline, 0.25mg, 0.5mg, 1.0mg) as the within-subject factor and condition (semaglutide, placebo) as the between-person factor. These count variables will be analyzed using a negative binomial MLM, however, this assumption will be tested and the modeling approach will be revised as needed to properly account for the nature of the outcome variable (e.g., zero-inflated negative binomial regression).

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics will be used to report relevant demographics such as age, sex, and education.

9.4.6 PLANNED INTERIM ANALYSES

No interim analyses of efficacy will be planned.

9.4.7 SUB-GROUP ANALYSES

Not applicable

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable

9.4.9 EXPLORATORY ANALYSES

Sex will be examined as an exploratory moderator in all analyses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the team will comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and adhere to ICH GCP. Consent will

be obtained by a study team member or other qualified staff member (e.g., RCMU) in person at the outset of the baseline session. Additional procedures are noted below.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

In obtaining and documenting informed consent, the team will comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and adhere to ICH GCP. Consent will be obtained remotely (via web teleconference and DocuSign, as described previously) by a qualified study staff member in person at the outset of the baseline session. Additional procedures are noted below.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The initial consent process will be conducted remotely using a HIPAA-compliant web platform (e.g., WebEx, Zoom, Teams) and Part 11-compliant DocuSign to maintain optimal safety. A copy of the consent form will be provided to the participant in advance of the scheduled videoconference. A qualified team member will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will electronically sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed (via DocuSign), before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the study is voluntary and the quality of their medical care will not be adversely affected if they decline to participate. While the initial consent form will be conducted electronically, supplementary consent forms (e.g., consent to unencrypted communication, HIPAA authorization, and biospecimen consent) may be conducted either remotely (via DocuSign) in advance of the baseline visit or in person (paper form) at the baseline visit, depending on timing.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. Circumstances that may warrant

termination or suspension include, but are not limited to determination of unexpected, significant, or unacceptable risk to participants. Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party. All research activities will be conducted in as private a setting as possible.

Any computerized data will be password protected and contained on a secure, password-protected computer or a secure server. Recruitment data (de-identified) will be stored in a secure, password-protected file accessible only to the study investigators and personnel. At the end of recruitment, eligible subject files will be separated from those failing to meet eligibility criteria, and records of ineligible recruitment subjects will be anonymized. Data pertaining to screening failures will be tabulated in an anonymized fashion. Data collected in other formats (e.g., medical screening notes) will be labeled only by study identifier and stored in binders in secure, locked cabinets while the study is taking place. Files will be stored and archived in accordance with Good Clinical Practice (GCP) standards. For all questionnaire and interview assessments, participants will be informed that they may decline to answer any question if they so choose.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored during the study for purposes of maintain contact with participants, and for communicating any safety information or unanticipated problems. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at UNC in the PI's laboratory and on secure backup servers with password-protected access. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Electronic data are stored on a password protected drive only accessible by the research team. Data obtained on paper will be transferred to an electronic data file (Excel, SPSS, REDCap), stored on a secure server, and identified by participants ID. For non-computer based forms, the data collection sheets are stored in a locked cabinet in a separate locked data storage space at the PI's laboratory.

At the end of the study, all study databases will be de-identified and archived in the PI's laboratory and backed up on a secure server hosted at UNC. De-identified data resulting from this study may also be

presented at meetings, published in journals or presentations. In addition, this study will be registered at ClinicalTrials.gov, and de-identified information from this study will be submitted to ClinicalTrials.gov.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the PI's laboratory. The study biostatistician will be given access to the data necessary for conducting specified analyses, and data will be de-identified prior to giving access.

De-identified biological samples will be stored at UNC for the duration of the study, until all biological tests are completed and the data transferred to electronic format. De-identified DNA samples will be stored indefinitely, provided the participant has given consent for DNA storage, in order to examine future questions related to phenotypes of interest for this line of research.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed (after specimens are de-identified).

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	Medical Monitor
<i>Christian Hendershot, Ph.D., Associate Professor</i>	<i>TBD (The medical monitor and DSMB members will be identified and added prior to data collection)</i>
<i>UNC-Chapel Hill</i>	
<i>104 Manning Dr.</i>	
<i>Christian_Hendershot@med.unc.edu</i>	
<i>Christian Hendershot, Ph.D., Associate Professor</i>	

The investigative team is summarized on the face page of this protocol. As noted, a DSMB will be formed prior to carrying out the study.

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will dictate the intervals at which they meet to assess safety and efficacy data. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the IRB and National Institutes of Health as necessary.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). A local study monitor will be appointed to provide on-site monitoring during the course of the research study.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

The PI will be responsible for addressing quality control issues and correcting errors or protocol deviations. The PI will have oversight over training study staff and ensuring that protocol elements are carried out with fidelity. Quality control will be ensured by developing SOPs for protocol elements to standardize data collection procedures. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

As a single-site, small-scale trial, the project will not involve coordinated data collection and management responsibilities across sites/teams. Data safety and storage precautions are outlined elsewhere in the study protocol.

10.1.8.2 STUDY RECORDS RETENTION

Study records will be retained for a minimum of 7 years following study completion. Paper source documents will be archived in accordance with UNC policies. Electronic materials and de-identified datasets will be stored securely as outlined above.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The PI will report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NIAAA Program Official and the IRB. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the PI.

10.1.11 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. All investigators will make a conflict of interest declaration at the outset of the study and at regular intervals thereafter in accordance with UNC policies.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

AASE	Alcohol Abstinence Self-Efficacy
AE	Adverse Event
APT	Alcohol Purchase Task
AUDIT	Alcohol Use Disorder Identification Test
BIS-11	Barratt Impulsivity Scale
BMI	Body Mass Index
BrAC	Breath Alcohol Concentration
CASE	Cigarette Abstinence Self-Efficacy
CES-D	Center for Epidemiological Studies Depression Scale
CEQ	Control of Eating Questionnaire
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CO	Carbon Monoxide
CPT	Cigarette Purchase Task
CRF	Case Report Form
CTRC	Clinical & Translational Research Center
DEQ	Drug Effects Questionnaire
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual for Mental Disorders v.5
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FPT	Food Purchase Task
FTND	Fagerstrom test for Nicotine Dependence
GCP	Good Clinical Practice
GLP-1	Glucagon-Like Peptide 1
GLP-1R	Glucagon-Like Peptide 1 Receptor
HbA1c	Glycated hemoglobin
ICH	International Conference on Harmonisation

ICS	Impaired Control Scale
IDS	Inventory of Drinking Situations
IRB	Institutional Review Board
MCQ	Monetary Choice Questionnaire
MNWS	Minnesota Nicotine Withdrawal Scale
MOP	Manual of Procedures
NC Tracs	North Carolina Translational & Clinical Sciences Institute
NDSS	Nicotine Dependence Syndrome Scale
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIH	National Institutes of Health
NRT	Nicotine Replacement Therapy
PACS	Penn Alcohol Craving Scale
PPC	Peak Provoked Craving
PI	Principal Investigator
POMS-SF	Profile Of Mood States Short Form
QA	Quality Assurance
QC	Quality Control
RBEDS	Reward Based Eating Drive Scale
RPI-EROS	Reward Probability Index – Environmental Reward Observation Scale
SAE	Serious Adverse Event
SAFTEE	Systematic Assessment for Treatment Emergent Effects
SNAQ	Simplified Nutritional Appetite Questionnaire
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SRE	Self-Report of the Effects of Alcohol Questionnaire
SUD	Substance Use Disorder
T2D	Type II Diabetes
TAS-20	Toronto Alexithymia Scale
TFEQ	Three Factor Eating Questionnaire
TLFB	Timeline Follow-Back Interview
TQSU	Tiffany Questionnaire of Smoking Urges
UP	Unanticipated Problem
UPPS-P	UPPS-P Impulsive Behavior Scale
WISDM	Wisconsin Inventory of Smoking Dependence Motives
WSWS	Wisconsin Smoking Withdrawal Scale
5-HT2C	Serotonin 2C Receptpr

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.2	July 26 2021	Elaboration on statistical analyses and clarification on other procedural issues.	Minor changes requested during initial review of the protocol.
1.3	Feb 28 2021	Clarification of medication dispensing procedures, addition of personnel, addition of DocuSign procedures, other protocol modifications.	Changes addressed issues that emerged while preparing for recruitment and meeting with IDS and study investigators.
1.4	June 23 2022	Minor revisions to exclusion criteria, and clarification of medication dosing and DSMB meeting plan	Refinement of study procedures and clarification of monitoring schedule as requested by DSMB and IDS
1.5	August 22 2022	Updates to medication storage, use of Phone.com for text messaging, select questionnaire modifications, modifications to alcohol self-administration session	Medication storage changes requested by IDS; Phone.com added as per UNC requirements for text messaging; other changes intended to streamline and improve assessment procedures
1.6	October 31 2022	Adjustments to inclusion criteria; added analysis for blood neutrophils; added additional recruitment flyers.	Changes made to facilitate recruitment and address an exploratory research question.

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