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Exenatide as an adjunct to nicotine patch for smoking cessation and prevention of postcessation weight gain among treatment-seeking smokers with pre-diabetes and/or overweight: study protocol for a randomised, placebo-controlled clinical trial

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ABSTRACT

Introduction Obesity and smoking are the two leading causes of preventable death in the USA. Unfortunately, most smokers gain weight after quitting. Postcessation weight gain (PCWG) is frequently cited as one of the primary barriers to a quit attempt and a common cause of relapse. Further, excessive PCWG may contribute to the onset or progression of metabolic conditions, such as hyperglycaemia and obesity. The efficacy of the current treatments for smoking cessation is modest, and these treatments have no clinically meaningful impact on mitigating PCWG. Here, we outline a novel approach using glucagon-like peptide 1 receptor agonists (GLP-1RA), which have demonstrated efficacy in reducing both food and nicotine intake. This report describes the design of a double-blind, placebo-controlled, randomised clinical trial that evaluates the effects of the GLP-1RA exenatide as an adjunct to nicotine patches on smoking abstinence and PCWG.

Methods and analysis The study will be conducted at two university-affiliated research sites in Houston, Texas, the UTHealth Center for Neurobehavioral Research on Addiction and Baylor College of Medicine Michael E. DeBakey VA Medical Centre. The sample will consist of 216 treatment-seeking smokers with pre-diabetes (haemoglobin A1c of 5.7%–6.4%) and/or overweight (body mass index of 25 kg/m² or above). Participants will be randomised (1:1) to receive subcutaneous injections of placebo or 2 mg exenatide, once weekly for 14 weeks. All participants will receive transdermal nicotine replacement therapy and brief smoking cessation counselling for 14 weeks. The primary outcomes are 4-week continuous abstinence and changes in body weight at the end of treatment. The secondary outcomes are (1) abstinence and changes in body weight at 12 weeks post end of treatment and (2) changes in neuroaffective responses to cigarette-related and food-related cues as measured by electroencephalogram.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial will examine the glucagon-like peptide 1 receptor as a novel target for smoking cessation and postcessation weight management.

⇒ This trial will use a randomised, double-blinded, placebo-controlled design with prespecified outcome measures and intention-to-treat analysis.

⇒ Building on our previous 6-week trial of exenatide, the current study will extend the treatment duration to 14 weeks and include a follow-up at 12 weeks post end of treatment.

⇒ By assessing neuroaffective responses to nicotine-related and food-related stimuli via electroencephalogram, the trial will provide a potential mechanism for the efficacy of exenatide in this population of smokers.

⇒ A potential limitation of the trial is the focus on smokers who are prediabetic and/or overweight, which may limit the generalisability of the findings.

INTRODUCTION

Obesity remains a major public health crisis with widespread impact on healthcare costs, quality of life and mortality. US prevalence data indicate that the majority (i.e. 74%) of American adults are overweight/obese - a
The probability of PCWG, compared with placebo. The resulted in a higher probability of abstinence and a lower and/or overweight, 6 weeks treatment with exenatide that in the sample of 82 smokers who were prediabetic and type 2 diabetes (T2D), potentially contributing to the first few months of quitting, and a non-trivial proportion of quitters gain more than 20 pounds. Postcessation weight gain (PCWG) is problematic for several reasons. First, concerns about PCWG prevent some people from initiating a quit attempt. Second, PCWG can be a cause of relapse. Third, PCWG can worsen metabolic health, leading to the development or progression of obesity and type 2 diabetes (T2D), potentially contributing to premature morbidity and mortality associated with these diseases.

Glucagon like peptide-1 (GLP-1) is produced in intestinal L-cells and released from the gut in response to food intake. By stimulating insulin secretion and inhibiting glucagon secretion, GLP-1 regulates postprandial glucose excursions. GLP-1 is also known to stimulate centrally mediated appetite control and satiety. Notably, GLP-1 receptor agonists (GLP-1RA) are currently used for the treatment of T2D and weight management in people with and without T2D. GLP-1 receptors are expressed in many brain regions. In addition to the hypothalamus and brain stem, GLP-1 receptors are expressed throughout the mesolimbic dopamine system, and GLP-1 containing neurons extend directly into the ventral tegmental area and nucleus accumbens. These brain regions are intimately associated with the regulation of food-related and nicotine-related reward. Consistent with this, preclinical studies have shown that GLP-1RAs significantly decrease nicotine self-administration and attenuate nicotine conditioned place preference. Further, our recent clinical trial of a GLP-RA extended-release exenatide showed that in the sample of 82 smokers who were prediabetic and/or overweight, 6 weeks treatment with exenatide resulted in a higher probability of abstinence and a lower probability of PCWG, compared with placebo. The objective of the current phase II clinical trial is to extend these promising findings by: (1) investigating the robustness of exenatide’s effects following a longer treatment and post-treatment period and (2) exploring putative mechanisms through which exenatide might facilitate smoking cessation and mitigate PCWG. Recent calls have been made for an experimental therapeutic approach to designing clinical trials in which the focus is not only on testing whether an intervention works but on gaining insight into how an intervention works through hypothesised target mechanisms.

### METHODS AND ANALYSIS

#### Study design

This clinical trial will use a randomised, double-blind, placebo-controlled design and will be conducted at two US sites, the University of Texas Health Science Center at Houston (UTHealth), Center for Neurobehavioral Research on Addiction (CNRA) and Michael E. DeBakey VA Medical Center (MEDVAMC). The sample will consist of 216 treatment-seeking adult smokers who have prediabetes and/or are overweight. Participants will be randomised (1:1) to receive exenatide, 2 mg or placebo (sterile saline, 0.9%), subcutaneously, once weekly for 14 weeks. All participants will receive nicotine replacement therapy (NRT, nicotine patches) for daily use and individual smoking cessation counselling. Participants will attend weekly clinic visits to receive exenatide/placebo and NRT and complete assessments of smoking frequency and quantity, breath carbon monoxide (CO) levels, weight and other assessments. Electroencephalogram (EEG) will be conducted at baseline and before the quit attempt to assess neuroaffective responses to food, nicotine and emotional stimuli. Primary outcomes (end-of-treatment abstinence and weight change) will be assessed at 12 weeks post-target quit day. Participants will return for a follow-up visit 12 weeks after the end of treatment (24 weeks post-target quit day) for the assessment of weight and smoking status.

#### Study aims

##### Specific aims

**Aim 1:** To determine if exenatide improves end-of-treatment smoking abstinence rates.

Hypothesis 1: Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence (self-reported and biochemically verified by expired breath CO levels) at 12 weeks post-target quit day. **Aim 2:** To determine if exenatide mitigates PCWG.

Hypothesis 2: Compared with placebo, treatment with exenatide will be associated with reduced PCWG at 12 weeks post-target quit day.

##### Exploratory aims

**Aim 3:** To assess the effect of exenatide on post-treatment abstinence and weight.

Hypothesis 3a: Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence (self-reported and biochemically verified) at 24 weeks post-target quit day.

Hypothesis 3b: Compared with placebo, treatment with exenatide will be associated with lower PCWG at 24 weeks post-target quit day.

**Aim 4:** To explore the effect of exenatide on neuroaffective responses to food-related, nicotine-related and emotional stimuli.

Hypothesis 4: Treatment with exenatide will be associated with an attenuation of event-related potential (ERP) reactivity specific to nicotine-related and food-related stimuli at week 3, relative to baseline ERP reactivity.
Participants
Eligibility
Participants will be 216 males and females between ages 18 and 75 years who report smoking 5 or more cigarettes per day for at least the past year and state a desire to quit smoking (defined as ‘intend to quit within 1 month’). Participants must have glycosylated haemoglobin (HbA1C) levels between 5.7% and 6.4% and/or a body mass index (BMI) of ≥25 kg/m².

The following exclusion criteria will be applied: (1) personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; (2) history of myocardial infarction, life-threatening arrhythmia or worsening angina pectoris; (3) severe gastrointestinal disease (ie, severe gastroparesis); (4) severe cardiovascular disease (history of myocardial infarction, life-threatening arrhythmia or worsening angina pectoris); (5) severe gastrointestinal disease (ie, severe gastroparesis); (6) creatinine clearance <45 mL/min or end-stage renal disease; (7) psychotic or bipolar disorder, or mood disorder with psychotic features, or eating disorder (existing diagnosis) or as determined by the structured interview; (8) moderate to high risk of suicidality; (9) psychoactive substance abuse or dependence (excluding nicotine dependence) within the past 3 months; (10) current use of glucose lowering medications; smoking cessation medications, medications used for weight management, or medications known to impact weight; (11) current use of chewing tobacco, snuff, snus or electronic cigarettes; (12) previous medically adverse reaction to study medications or nicotine; (13) women who are currently pregnant or lactating, or of child-bearing potential and are not using medically accepted forms of contraception and (14) any illness or condition which in the opinion of the principal investigator (PI) and/or the study physician would preclude safe and/or successful completion of the study.

Discontinuation/withdrawal criteria
The participant may be discontinued at any time during the study at the discretion of the PI and/or the study physician for safety, behavioural, compliance or administrative reasons. Efforts must be made to have the participants, who discontinue the study medication, to continue in the study. Only participants who withdraw consent will be considered as withdrawn from the study.

Screening
Participants will be recruited using various strategies, including flyers, posters, newspapers and companies that provide recruitment services for clinical research using online platforms. Potential participants will complete a brief telephone prescreen to determine initial eligibility. The prescreen assessment includes questions assessing medical and psychiatric history, psychoactive substance use and smoking history. Based on the initial prescreen, individuals who appear eligible will be invited for a face-to-face screening visit.

The screening will begin with the completion of the informed consent (see online supplemental material) which will be obtained by the PI or designee. Informed consent procedures will include details of the study, potential risks, study timeline and voluntariness of participation and dropping out. Following informed consent, each participant will complete demographic, medical and smoking history assessments and undergo a psychiatric evaluation and physical examination. Blood samples will be collected to examine complete blood count (CBC), comprehensive metabolic panel (CMP), pancreatic enzymes and HbA1C levels. Urine samples will be collected to assess cotinine levels and to rule out drug use and pregnancy (in women of childbearing potential).

Study visits
After determining study eligibility, qualified participants will return to the clinic once a week for 14 treatment visits. Visits will include assessments of vital signs, adverse events (AEs) and concomitant medications; administration of exenatide/placebo and dispensation of nicotine patches for the upcoming week; smoking cessation counselling; and completion of various assessments as detailed in the Data collection and measures subsection and table 1.

Randomisation
The allocation orders, represented by a randomly assigned blinding coded letter for each treatment condition, will be generated with a pseudorandom number generator and uploaded to an electronic database (REDCap), which will be used to implement randomisation at both sites. The allocation ratio will be 1:1 (exenatide, placebo) and imbalanced randomised orders will be rejected to maintain balanced recruitment.

Participants, investigators and care givers performing assessments and persons performing data analysis will remain blinded to the participants’ assigned conditions (exenatide, placebo). An unblinded study nurse will maintain a hard copy of the blinding codes for each treatment condition in a secure, locked location. A password-protected field will also be uploaded to REDCap that maintains the unblinding codes if emergency unblinding is required.

Intervention
Exenatide/placebo
Exenatide will be purchased commercially as Bydureon for subcutaneous injection and administered at a dose of 2 mg once a week for a total of 14 weeks (2 weeks before the target quit day and 12 weeks post-target quit day). Exenatide is supplied as a powder with a solvent for once-weekly injection. Each single-dose, dual-chamber pen contains 0.65 mg of diluent and 2 mg of exenatide, which remain isolated until mixed. An unblinded study nurse not involved in behavioural counselling, data collection or outcome measurement will prepare and administer medication. Patients will be blindfolded while receiving the injections.
Sterile saline (0.9%) will serve as the placebo for exenatide. The placebo will be administered in the same manner and volume as exenatide using insulin syringes.

Nicotine replacement therapy

Nicotine patches (generic) will be purchased commercially and dispensed during clinic visits for 1 week of use.\textsuperscript{27} Participants will be instructed to use one patch daily starting 2 weeks before their target quit day for a total of 14 weeks. Participants who smoke >10 cigarettes/day will use 21 mg patches for the first 12 weeks, 14 mg patches for week 13 and 7 mg patches for week 14. Participants who smoke 5–10 cigarettes per day will use 14 mg patches.

### Table 1: Study design and assessment schedule

<table>
<thead>
<tr>
<th>Phase →</th>
<th>Screen</th>
<th>Run-in</th>
<th>Treatment period</th>
<th>F/U</th>
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</thead>
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</tr>
<tr>
<td>Approximate day →</td>
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<td></td>
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<tr>
<td>Visit →</td>
<td>0</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baseline, eligibility and safety measures

- Consent, demographics, medical history, physical exam, psych (MINI)
- Smoking status (FTND, urine cotinine)
- Vital signs, prior and concomitant meds
- AE/SAE

Medications and adherence

- Randomisation
- Exenatide/placebo administration
- Nicotine patch dispensation
- Nicotine patch adherence

Smoking-related measures and analyses

- Breath CO
- Smoking frequency and quantity (TLFB)
- Withdrawal and craving (WSWS, QSU, mCEQ)
- 4 week continuous abstinence
- 7 day point prevalence abstinence

Weight-related and diet-related measures

- Weight
- BMI
- Waist circumference
- Weight concerns and efficacy (WCS, WEAKS)
- Food craving (FCI)
- Diet and physical activity (ASA24, GPAQ)

Other measures (self-report and mechanism)

- Psychiatric (PANAS, PHQ-8)
- Mechanism (EEG)
- Laboratory assessments
- Urine drug screen, urine cotinine, CBC, CMP, amylase, lipase
- HbA1C
- Lipid panel
- Fingerstick blood glucose
- Urine pregnancy test

AE, adverse event; ASA24, Automated Self-Administered 24 hours Dietary Assessment Tool; BMI, body mass index; CBC, complete blood count; CMP, complete metabolic panel; CO, carbon monoxide; EEG, electroencephalogram; FCI, Food Craving Inventory; FTND, Fagerstrom Test for Nicotine Dependence; F/U, follow-up; GPAQ, global physical activity questionnaire; HbA1C, glycosylated haemoglobin; mCEQ, Modified Cigarette Evaluation Questionnaire; MINI, Mini-International Neuropsychiatric Interview; NRT, nicotine replacement therapy; PANAS, Positive and Negative Affect Schedule; PHQ, Patient Health Questionnaire; QSU, Questionnaire of Smoking Urges; SAE, serious AE; TLFB, time line follow back; WCS, Weight Concern Scale; WEAQS, Weight Efficacy after Quitting Scale; WSWS, Wisconsin Smoking Withdrawal Questionnaire.
for the first 12 weeks and 7 mg patches for weeks 13 and 14.28 To estimate patch adherence, participants will be instructed to return all used and unused patches.29 Patch adherence will be defined as wearing the patch for ≥6 of 7 days/week across the 14 weeks.30 31

Discontinuation of the study medication
Discontinuation of the study medication can be decided by either the PI or the participant. Participants who discontinue the study medication will be encouraged to continue with the scheduled visits and assessments to ensure continued counselling and data collection.

Smoking cessation counselling
All participants will receive brief individual behavioural smoking cessation counselling based on the US Clinical Practice Guidelines, as recommended for use with pharmacotherapy.32 Counselling will not include recommendations on weight management strategies to directly assess the pharmacological effect of exenatide on changes in weight. The manual-driven counselling protocol has been used in previous studies33–35 and consists of once a week in-person sessions and 2 brief (10–15 min) supportive phone calls (at prequit and again at 3 days postquit), spanning the 14-week active treatment phase. Counseling will be provided by master’s level clinicians who will be trained by a clinical psychologist (JS) with extensive experience in developing counselling protocols and evaluating behavioural treatment fidelity in clinical trials of substance use disorders.36 37 Counselling sessions will be audiotaped, with 20% of sessions randomly selected to assess adherence and competence.38

Participant adherence to study procedures
Throughout the study, the study staff will remind the participants to follow the study procedures and requirements to ensure participant compliance. If a participant is found to be non-compliant, the she/he will be reminded regarding the importance of following the instructions given.

Data collection and measures
Please refer to table 1 for time points.

Smoking-related assessments
Baseline smoking status will be assessed via self-reported smoking of ≥5 cigarettes/day for ≥1 year and confirmed by a urinary cotinine test.

Nicotine dependence will be assessed using the Fagerstrom Test for Nicotine Dependence.39

Smoking frequency and quantity will be assessed using the time-line follow-back (TLFB) interview methodology.40

Breath CO will be assessed using a CO monitor (MicroSmokerlyzer, Williamsburg, Virginia USA).

Withdrawal symptoms will be assessed using the Wisconsin Scale of Withdrawal Symptoms (WSWS).41

Craguing for cigarettes will be evaluated using the Questionnaire of Smoking Urges (QSU).42

Smoking satisfaction and psychological reward from smoking in subjects who report smoking between the visits will be evaluated using the Modified Cigarette Evaluation Questionnaire (mCEQ).43

Weight-related and diet-related assessments
Weight (kg) will be measured without shoes using a medical grade digital scale. Height (cm) will be measured without shoes using stadiometer. Waist circumference (cm) will be measured without clothes, midway between the lower rib margin and iliac crest44 using measure tape.

Baseline weight concerns and weight efficacy (ie, self-efficacy for preventing PCWG) will be assessed during the screening visit using the Weight Concern Scale (WCS)7 and Weight Efficacy after Quitting Scale,7 respectively.

Diet will be assessed using the Automated Self-Administered 24-hours Dietary Assessment Tool.45

 craving for food will be assessed using the Food Craving Inventory (FCI).46

Physical Activity will be assessed using the WHO Global Physical Activity Questionnaire.47

Psychiatric/substance use assessments
Psychiatric/substance use history will be assessed using the Mini-International Neuropsychiatric Interview.48

Depressive Symptoms will be assessed using Patient Health Questionnaire-8 (PHQ-8).49

Positive and negative affect will be assessed using the positive and negative affect schedule (PANAS).50

Laboratory assessments
Blood tests will include analyses of CBC, CMP, pancreatic enzymes (amylase and lipase), HbA1C, lipids and fingerstick blood glucose; urine tests will include analysis of cotinine, drug screen and pregnancy test in women of childbearing potential; and breath tests will include assessments of CO levels.

EEG will be recorded with a 64-channel actiCAP active electrode cap, amplified with BrainAmp MR and digitised with Brain Vision Recorder (CNRA) or amplified with actiCHamp and digitised with PyCorder (MEDVAMC) (Brain Products, Munich). Procedures for data collection and data reduction will be similar to those used in previous studies.51–56 For each participant, the average ERP will be computed at each scalp site for each category (ie, pleasant, unpleasant, neutral, food and cigarette related) and, in line with previously published reports57 58 and methodological recommendations,59 the amplitude of the late positive potential (LPP) between 400 and 800 ms over a priori selected central and parietal sites will be computed. The steps outlined above for the EEG/ERP data reduction and the statistical analyses on the EEG will be performed using software (ie, BESA, Brain Vision Analyzer, SPSS, STATA, SAS and R) tested in previous studies.


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Outcome measures

Primary outcomes
1. Percentage of participants with 4-week continuous abstinence at 12 weeks post-target quit day, defined as no smoking, not even a puff, as measured by self-report (TLFB) and biochemically verified (CO ≤5 ppm).
2. Weight change in kilograms at 12 weeks post-target quit day.

Secondary outcomes
1. Percentage of participants with 4-week continuous abstinence at 24 weeks post-target quit day as measured by self-report (TLFB) and biochemically verified (CO ≤5 ppm).
2. Weight change in kilograms at 24 weeks post-target quit day.
3. Amplitude of the late positive potential evoked by visual stimuli.

Other outcomes
1. Seven-day point prevalence abstinence at 12 and at 24 weeks post-target quit day.
2. Changes in BMI, waist circumference, HbA1C and serum triglyceride levels.
3. Smoking satisfaction (mCEQ score) in participants who report smoking between visits.
4. Craving for cigarettes (QSU score).
5. Withdrawal symptoms (WSWS score).
6. Craving for highly palatable food (FCI score).
7. Depressive symptoms (PHQ-8 score) and affect (PANAS score).

Safety and monitoring

Medical monitoring
Vital signs and overall well-being will be assessed at each visit. Blood glucose levels will be assessed prior to each dose of exenatide. Subsequent doses of the study medication will not be administered if any of the following occur or suspected: acute pancreatitis, hypoglycaemia (blood glucose <70 mg/dL), severe injection site reaction, hypersensitivity reaction, anaphylaxis, angioedema, acute kidney injury or if the study physician believes that there may be any reason to withhold the study medication.

AE assessment and management
Careful clinic procedures will be followed to avoid any potential harm to participants from possible adverse medical or psychological reactions. At each visit, participants will be asked by the study staff if they are experiencing any discomfort or symptoms that might indicate potential side effects of exenatide or NRT. Participants will be withdrawn from study participation if they show signs of serious adverse reactions that pose a threat to their physical or psychological health. Any symptoms or complaints, solicited or spontaneously reported, will be recorded and reported to the IRB and NIDA if events are classified as serious.

Data collection, entry and storage
Checklists will guide study personnel in all procedures for data collection and data management. Whenever possible, questionnaire data are entered directly into the computer by the participant, reducing data entry error. All neurobehavioral data are collected automatically by the computer using professional programmes designed for this purpose and does not allow missing or impossible values. All hand-entered data (miscellaneous study forms) are initially reviewed by the study coordinator for general accuracy and completeness. They are then double entered in REDCap, with any inconsistencies examined and resolved. Data quality will be monitored continuously by the quality control manager and any problems detected will be discussed with the PIs. If necessary, retraining of data collectors will be conducted. Only investigators will have access to the data.

Data security and plan for protecting confidentiality
All data collected on paper forms will be stored in locked cabinets, while electronic data will be stored in REDCap database on a secure password-protected server maintained by the UTHHealth Medical School Information Technology Department. Individual participants and their research data will be identified by a unique study identification number (study ID). The study data entry and study management systems will be secured and password protected. The participants’ contact information will be securely stored for internal use during the study. 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 IRB and institutional regulations.

Data monitoring
The study PI and research team will monitor data on ongoing basis. In addition, a data safety and monitoring board (DSMAB) will oversee the ongoing progress of the study. The board consists of two physicians, a psychologist and a biostatistician who are not affiliated with the study or the sponsor. Each member will provide written documentation attesting to absence of conflict of interest. The initial responsibility of the DSMAB is to review and approve the initiation of the trial. Thereafter, DSMAB evaluations will be conducted on the annual basis. On the study completion, the DSMAB will perform end-of-study evaluation. An emergency meeting of the DSMAB (open, closed or executive session) may be called at any time by the Chairperson should questions of patient safety arise.

Trial stopping rules
The trial may be suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension include, but are not limited to determination of unexpected, significant or unacceptable risk to participants; insufficient compliance to protocol requirements; and/or data that are not sufficiently complete and/or evaluable. If the study is suspended, it may resume once
concerns about safety, protocol compliance and data quality are addressed and satisfy the suspending party and the IRB.

**Protocol modifications**

The study PI will receive IRB approval before initiating any changes, including those required by the sponsor, which would affect study participants, such as changes in methods or procedures, numbers of kinds of the study participants, or revisions to the informed consent document or procedures. All protocol revisions will be submitted to the primary sponsor of research.

**Project timeline**

The recruitment for the study began on 7 December 2022; and the estimated primary completion date (final data collection for primary outcome measures) is 31 March 2026. It is anticipated that each site will recruit a minimum of 3 participants (6 participants between the two sites) per month for a total of 216 participants during the 36-month enrolment period. Once randomised, participant duration is 26 weeks.

**Power calculation and sample size**

**Assumptions**

Power considerations for the current trial were calculated to assess the effect of treatment on the primary outcomes in hypothesis 1 (4-week continuous abstinence) and hypothesis 2 (PCWG). Calculations were based on generating k=1000 normal approximations to the Bayesian posterior distribution via Monte Carlo simulation in the R Statistical Computing Environment. Statistical power was conceptualised as the percentage of the posterior distributions that met or exceeded a specific probability threshold (described below). All calculations assumed n=172 to account for 20% attrition. Regarding the placebo group effect size for NRT monotherapy (patch <22 mg) in hypothesis 1, the probability of abstinence was set to 0.505.

**Simulation results**

Analyses will focus on posterior probabilities ≥0.70 that the effect of exenatide (relative to control) exists for both abstinence and weight. For hypothesis 1, given the assumptions above, calculations determined that the posterior probability met or exceeded 0.70 in 80.3% of simulations where an absolute difference in the probability of abstinence for control (0.305) was 10% lower than that for exenatide (0.405). For hypothesis 2, the same sample size met or exceeded the probability threshold in 84.3% of simulations when assuming a group difference in weight at the end of treatment as small as Cohen’s d=0.20. This study is thus powered to detect a posterior probability PP ≥70% that exenatide confers at least 10% improvement in abstinence as well as a minimum effect size Cohen’s d=0.20 for lower weight at the end of treatment.

**Statistical analysis plan**

**Descriptive statistics and confounding variables**

Descriptive statistics will evaluate measures of central tendency and frequencies for all continuous and categorical variables (respectively) measured in the study. Preliminary data analyses will inspect relationships between sample characteristics, treatment condition and outcome variables via traditional statistical tests (e.g., $\chi^2$; Mann-Whitney; t-tests). Any sample characteristics that demonstrate a relationship with both treatment and the outcome variable in a given model meet criteria for being a potential confounder. Sample characteristics that will specifically be evaluated as potential confounders include sex, age, socioeconomic status, smoking heaviness and nicotine dependence, patch adherence, diet, physical activity, baseline BMI, and baseline weight concerns and weight efficacy. Any characteristic that meets the criteria as a potential confounder will result in two models: one with covariate adjustment for that characteristic and a simple model without adjustment. If adjustment does not affect inferences regarding the primary predictor-outcome relationship, the simple model will be retained. If the inferences change, we will report both models. All models will statistically control for the effect of site.

**Inferential paradigm**

Analyses will use Bayesian statistical inference to directly yield the probability of an alternative hypothesis given specified prior information. Weakly informative priors will be used as a default (e.g., $b$; $\sim N[\mu=0,\sigma^2=100]$; for non-linear outcome variables this prior applies to the coefficient within the link-function). Sensitivity analyses using optimistic and pessimistic, sceptical priors will evaluate prior assumptions. Informative priors will use extant information (e.g., meta-analytical findings for smoking outcomes). Analyses will use effective sample size and scale reduction factors to assess convergence.

**Statistical modelling**

Analyses will primarily use generalised linear modelling (GLM) with multilevel components (GLMM) for correlated observations. Multilevel models will incorporate random effects (e.g. a level 2 intercept for correlated observations) as needed. Potentially non-linear relationships between predictors and outcomes will be evaluated via inclusion of polynomial or spline effects. Evaluation of distributional assumptions will use residual plots, formal statistical tests and posterior predictive checking. Violations of assumptions will be addressed via transformation, robust estimation, stratification and/or coefficient scaling where appropriate. GLM/GLMM will be performed using the R statistical computing environment via rstan and brms.

**Missingness, multiplicity and secondary analyses**

**Intention-to-treat analyses**

Will be conducted to provide estimates of treatment effects that are unbiased with respect to non-random drop
out. Individuals that drop out of the trial will be imputed as continuing to smoke. A per-protocol secondary analysis will provide an optimistic estimate of treatment effects. Missing data will be addressed via explicit modelling of missingness or imputation where appropriate. Each approach is robust to ignorable missingness (ie, missing completely at random (MCAR) and missing at random (MAR)). Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions. Due to its observation of the likelihood principle,70 Bayesian approaches will evaluate longitudinal changes in weight between groups over time.

Specific analyses
Specific aim 1: hypothesis 1
Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence (self-reported and biochemically verified) at 12 weeks post-target quit day. GLM will evaluate 4-week continuous abstinence (yes vs no) as a function of treatment condition. Follow-up analyses will evaluate the trajectory of abstinence over time via GLMM.

Specific aim 2: hypothesis 2
Compared with placebo, treatment with exenatide will be associated with reduced PCWG at 12 weeks post-target quit day. GLM will evaluate residual change by modelling end of treatment weight as a function of treatment condition, controlling for baseline. GLMM will evaluate follow-up analyses of longitudinal changes in weight between groups over time.

Exploratory aim 3: hypothesis 3a
Compared with placebo, treatment with exenatide will result in a higher rate of 4-week continuous abstinence at 24 weeks post-target quit day. Analyses follow from those stated above for hypothesis 1, with the outcomes evaluated at 24 weeks post-target quit day instead of 12 weeks. GLM will evaluate 4-week continuous abstinence (yes vs no) as a function of treatment condition, and GLMM will evaluate the trajectory of abstinence over time.

Exploratory aim 3: hypothesis 3b
Compared with placebo, treatment with exenatide will be associated with a lower PCW at 24 weeks post-target quit day. Analyses follow from those stated above for hypothesis 2, with the outcomes evaluated at 24 weeks post-target quit day instead of 12 weeks. GLM will evaluate residual change by modelling treatment weight as a function of treatment condition, controlling for baseline, and GLMM will evaluate longitudinal changes in weight between groups over time.

Exploratory aim 4: hypothesis 4
Treatment with exenatide will be associated with an attenuation of ERP reactivity specific to nicotine-related and food-related stimuli at week 3 relative to baseline. Multivariate GLM will evaluate patterns of responses across different types of stimuli as a function of treatment group.

Interim analyses
Not applicable for this trial.

Patient and public involvement
None.

Ethics and dissemination
The study approval has been received from the UTHHealth Committee for the Protection of Human Subjects (HSC-MS-21-0639) and Baylor College of Medicine Institutional Review Board (H-50543). All participants will sign informed consent. The study is registered on ClinicalTrials.gov, NCT05610800. The study results will be disseminated via peer-reviewed publications and conference presentations.

DISCUSSION
Preclinical data showing that GLP-1RAs attenuate the reinforcing effects of food and nicotine, coupled with the results of the first human study that demonstrated the positive effects of exenatide treatment on smoking and weight outcomes, provide a strong premise for targeting GLP-1 receptors to facilitate smoking abstinence and mitigate PCWG. Building on our previous 6-week trial of exenatide,25 the current study will include a longer, 14-week, treatment duration and a post-treatment follow-up at 12 weeks after the end of treatment. In addition to examining the impact of exenatide on smoking abstinence and PCWG, this trial will explore putative mechanisms by which exenatide might modulate smoking and weight outcomes. The most compelling preclinical evidence to date suggests attenuation of responding in brain networks related to reward processing as a plausible mechanism of action. By measuring ERP reactivity to nicotine-related and food-related stimuli, we aim to interrogate reward-relevant cortical regions by which exenatide might reduce smoking and mitigate PCWG.

We note three key limitations of this study. First, the trial’s focus on individuals with pre-diabetes and/or overweight may limit the generalisability of the findings. Second, administration of the study medication during in-clinic visits will not allow assessment of acceptability and adherence to a subcutaneously administered therapy for smoking cessation and weight management in the real world. Third, the 14-week treatment duration and the 12-week post-end-of-treatment follow-up periods are relatively short. If the hypotheses of this study are confirmed, subsequent research would require examination of exenatide over a longer treatment period and a post-treatment
follow-up to ascertain the optimal length of therapy and the sustainability of exenatide's effects.

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**Contributors** According to the definition given by the International Committee of Medical Journal Editors, all the authors qualify for authorship. LY designed the study and wrote the first draft of the study protocol. CDV, FV and JS made substantial contributions to the overall study design. FV and HEW designed the EEG paradigm. PMC developed the smoking cessation counselling protocol. RS undertook the statistical power calculation and statistical analysis plan. LY wrote the first draft of the manuscript based on the study protocol. CDV, FV, RS, MFW, TK, HA, SBL and JS contributed with manuscript revisions and important intellectual content. All authors have approved the final manuscript.

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