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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: O Cobb C, Jonathan Foulds J, Yen M-S, et al. Effect of an electronic nicotine delivery system with 0, 8, or 36 mg/mL liquid nicotine versus a cigarette substitute on tobacco-related toxicant exposure: a four-arm, parallel-group, randomised, controlled trial. *Lancet Respir Med* 2021; published online April 12. http://dx.doi.org/10.1016/S2213-2600(21)00022-9.

Supplementary Appendix

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Supplementary Methods

Contributions of authors

JF, TE, CB, and SV conceived the original idea for the trial and sought and obtained funding. JF, TE, CB, SV, JY, M-SY, AL, and CC contributed to the writing of the study protocol. JF, TE, M-SY, CC, LK, and SS (member of the CSTP-Randomized Control Trial Methods Workgroup) contributed to the writing of the statistical analysis plan. M-SY did all data analyses with consultation from LK, CC, and SS. CC and M-SY accessed and verified the underlying data. The first draft of the paper was written by CC with input from all co-authors. CC is the guarantor for this paper. All authors read and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Members of the CSTP-Randomized Control Trial Methods Workgroup contributed to designing the study protocol and/or collecting the data.

Study Protocol and Statistical Analysis Plan

A complete study protocol and summary of changes made after initiation of the study is available by request. A published version of the study protocol and original statistical analysis plan is publically available.[1] A copy of the final statistical analysis plan is found at the end of this appendix.

Study products and blinding

Electronic nicotine delivery system (ENDS) liquid (0, 8, and 36 mg/ml) was purchased from an ENDS retailer located in Richmond, VA and had nicotine concentration verified by an independent laboratory prior to use (BLQ for 0 mg/ml; +/-1 mg/ml for 8 mg/ml; +/- 2 mg/ml for 36 mg/ml). Following nicotine concentration verification, ENDS liquid was split between sites and shipped as needed for dispensation.

Cartomizer preparation and dispensation procedures were identical between sites and utilized paper-based logs as well as electronic records to ensure blinding as well as accurate product assignment. Administrative staff with no participant contact prepared all cartomizers for dispensation (1 mL of liquid per cartomizer). All filled cartomizers were stored with the cartomizer mouth-end upright in child-proof plastic vials (7 cartomizers per vial). Filled cartomizers/vials were discarded after 27 days to ensure cartomizers more than 4 weeks old were not given to participants. This procedure was used to as a quality control measure considering some study visits were approximately 4 weeks apart. When dispensed, child-proof plastic bottles (not cartomizers) were labeled with an adhesive sticker by administrative staff that indicated participant ID, liquid flavor, visit number, and date of cartomizer expiration.

Following randomisation to the cigarette substitute condition, researchers reviewed and provided participants with a copy of their study product manual along with two cigarette substitutes. Manual instructions also included the following text: “For best results - Practice using your cigarette substitute (including trying different airflow settings) to find a method that works best for you.”

Following randomisation to an ENDS condition, researchers reviewed and provided participants with a copy of their study product manual along with two pre-charged ENDS batteries, a charger, and carrying case. The ENDS manual provided detailed information on what participants were given, how to set up the ENDS (i.e., attach/replace the cartomizer, use the button to activate the heating element, safely store their study product), how to maintain their daily tobacco use diary, and some potential ENDS related side effects. Manual instructions also included the following text: “For best results - Practice using your ECIG to find a method that works best for you, consistent with local rules and regulations regarding clean indoor air.” Following manual review, researchers then asked participants to sample two cartomizers corresponding to tobacco and menthol flavor of their assigned condition (i.e., liquid nicotine concentration was consistent with condition assigned). Participants were informed that they would receive the selected ENDS flavor for the duration of the study. Following sampling and flavor selection, researchers retrieved the participant’s full supply of cartomizers for that visit.

Of note all participants had the opportunity to experience the alternate study product to which they were randomised at the 24-week visit (end of the intervention period). Individuals initially randomised to an ENDS condition received two cigarette substitutes and a study product manual at week 24. Individuals initially randomised to a cigarette substitute condition were provided with 21 cartomizers (always at 0 mg/ml; flavor consistent with cigarette menthol preference), 1 ENDS battery/charger/carrying case, and a study product manual.

Each ENDS+liquid concentration was tested in a clinical laboratory study using the same ENDS, cartomizer, and liquid with identical characteristics.[1] When experienced END users were asked to take 10 puffs, 8 mg/ml liquid resulted in a boost of 8.2 ng/ml (SD=7.8), and 36 mg/ml liquid resulted in a boost of 17.9 ng/ml (SD=17.2). When ENDS-naive cigarette smokers asked to take 10 puffs, 8 mg/ml liquid did not result in a significant increase in plasma nicotine relative to baseline, and 36 mg/ml liquid resulted in a boost of 6.8 ng/ml (SD=7.1).[2]

Measures

The following measures were administered during 1 or more of the 12 in-person visits: nicotine withdrawal symptoms[3,4], environmental smoke exposure[5], cigarette and study product dependence ([6]; scores range from 0 to 20, with higher values indicating greater dependence), drug and alcohol use[7,8], mood/stress[9-11], respiratory/cardiovascular disease risk factors[12,13], study product evaluation items ([14]).

Biological Measures

Urinary total NNAL and cotinine analyses were performed using validated methods performed by the Bioanalytical Shared Resource Laboratory at Virginia Commonwealth University.

Statistical Analysis

We first examined all baseline demographics and participant characteristics to identify any baseline imbalances after randomisation (see Table S1). Discrete variables were summarized by frequencies with percentages and compared using Chi-squared test or Fisher’s exact test when appropriate. Continuous

variables were summarized by mean with standard deviation, median with interquartile range, or geometric mean with 95% confidence interval, and compared using one-way ANOVA or nonparametric Kruskal-Wallis test. Normality of data was examined using graphical methods (e.g., Q-Q plot) or Kolmogorov-Smirnov test. The Box-Cox transformation was applied to non-normal data including urinary total NNAL and urinary cotinine (both were standardized by creatinine prior to transformation).

Our analysis sample included four outcomes – urinary total NNAL, urinary cotinine, exhaled carbon monoxide (CO) and cigarettes smoked per day collected during the intervention period (week 0-24), and participant characteristics collected at baseline (week 0, see details in Table S1). We employed multiple imputation to impute missing values in both the four outcomes and the participant characteristics included in the adjusted analysis models.

The multiple imputation included 2 steps. First, to account for reasons contributed to attrition, we examined the association between missingness of urinary total NNAL (primary outcome) and baseline participant characteristics described in Table S1 using Chi-squared test or Fisher's exact test. Second, baseline characteristics significantly associated with NNAL missingness were included in a fully conditional regression model[15] along with several covariates that we deemed essential, including study site, gender, age and race/ethnicity. Detailed covariates are listed in Table A below. Five completed imputation data sets were created by the fully conditional model and each consists of completed outcomes (urinary total NNAL and urinary cotinine at weeks 0, 4, 12 and 24; exhaled CO and cigarettes smoked per day at weeks 0, 1, 2, 4, 8, 12, 16, 20 and 24) and completed baseline covariates.

After missing value imputation, linear mixed-effect models were used for both primary unadjusted analyses and secondary adjusted analyses to assess the variations of the outcomes across conditions and over time. Time, condition, and their interaction were included as fixed effects in both primary unadjusted analyses and secondary adjusted analyses. A random effect was included to account for within-participant dependence. In the adjusted model, study site, gender, age and race/ethnicity were always included as covariates of interest. Additional outcome-specific covariates included the adjusted models were selected through a stepwise model selection procedure and are listed in Table B below. Linear mixed-effect models were applied to all five imputation data sets. Results from each data set were pooled to produce inferential results (SAS procedure name: PROC MIANALYZE).

Table A. Covariates included in fully conditional regression model

	Covariates
Fully conditional regression model for all outcomes	Study site, gender, age, race/ethnicity, education, total household income, age of smoking initiation, week 0 environmental smoke score, week 0 urinary total NNAL (transformed, pg/mg creatinine), week 0 urinary cotinine (transformed, ng/mg creatinine), week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 body mass index, week 0 height, week 0 weight, week 0 hip circumference, week 0 waist circumference, week 0 diastolic blood pressure, week 0 Center for Epidemiologic Studies Depression Scale score, week 0 Clinical Chronic Obstructive Pulmonary Disease score, week 0 partial INTERHEART non-laboratory score, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, week 0 Perceived Stress Scale score, week 0 forced expiratory volume in one second, and week 0 forced vital capacity

Table B. Covariates included in secondary adjusted analyses

Covariates included in secondary adjusted analyses	
Adjusted model for urinary total NNAL	Study site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed)
Adjusted model for urinary cotinine	Study site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score
Adjusted model for exhaled CO	Study site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second
Adjusted model for cigarettes smoked per day	Study site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second

Pairwise comparisons with Bonferroni adjustment were conducted 1) between conditions at each time point (6 comparisons; alpha=0.008) and 2) within conditions relative to week 0. Bonferroni adjusted alpha was 0.017 for comparisons relative to week 0 in urinary total NNAL and urinary cotinine (3 comparisons), and 0.006 for comparisons relative to week 0 in exhaled CO and CPD (8 comparisons).

Sensitivity analyses were performed under unadjusted and adjusted conditions, with or without missing data imputation. In the intent-to-treat (ITT) analysis, all available data was considered with no imputation on missing values. The per-protocol (PP) analysis only included participants who had the desired outcome completed at weeks 0, 4, 12 and 24. In the baseline-carried-forward (BCF) and the last-observation-carried-forward (LOCF) analyses, missing values were replaced with the week 0 observation and the last available observation of the participant, respectively.

A dichotomized outcome was defined to assess study product use (ENDS/CS) by using the 7-day TLFB data. Based on this latter measure, if participant reported no use of their study product in the past 7 days prior to the visit then study product use status for the visit was no use, otherwise the study product use status was yes. ITT analyses were performed, including with or without an assumption of no use for participants with missing 7-day TLFB data. Additionally, a PP analysis was performed using participants with available study product use status at weeks 0, 4, 12, and 24. Pairwise comparisons between conditions and relative to week 0 were conducted with appropriate Bonferroni adjustments.

Supplementary Results

Overview

Results of secondary adjusted analyses, sensitivity analyses, pairwise comparisons, and summary of adverse events are included in supplementary results.

Figures S3-14 present the estimates and 95% confidence intervals based on the mixed-effect models for secondary adjusted analyses and sensitivity analyses.

Table S3 compares the demographics and week 0 participant characteristics between participants who completed the study period (week 0-24) and who did not.

Table S4 details the retention and reasons for withdrawal over the trial.

Table S5 summarizes significant pairwise comparisons between conditions and relative to baseline for each outcome by analysis approach.

Tables S6-64 present the estimates, 95% confidence intervals and p-values of pairwise comparisons between conditions and relative to baseline within conditions for urinary total NNAL, urinary cotinine, exhaled CO, and cigarettes smoked per day.

Tables S66-74 present the percentages and p-values of pairwise comparisons between conditions and relative to baseline within conditions for study product use.

Tables S75-78 present a descriptive analysis of adverse events.

Differences among multiple imputation, intention-to-treat and baseline-carried-forward analyses

To justify if missing not at random or informative missingness were observed in our data, we specifically compared the results from multiple imputation (MI), intent-to-treat (ITT) and baseline-carried-forward (BCF) analyses. ITT served as an analysis on all available data without assumption, and BCF served as the most conservative imputation of missing values.

Urinary Total NNAL

A significant difference between CS and 36 mg/ml at week 24 was consistently observed in adjusted models using MI, ITT, and BCF methods and was only found in MI unadjusted model. A significance difference between 0 mg/ml and 36 mg/ml at week 24 was only observed in BCF adjusted model but not in the other two methods. Compared to baseline (week 0), a significant difference at week 12 in 36 mg/ml was carried through week 24 in all three methods in unadjusted and adjusted models.

Urinary Cotinine

Adjusted models using ITT and BCF methods revealed a significant difference between 8 mg/ml and 36 mg/ml at week 4, but the adjusted model using MI method did not detect this difference. On the other hand, the significant difference between week 12 and baseline (week 0) in CS was only observed in MI adjusted model but not in the other two methods. None of the unadjusted models from the three methods detected the significant differences above. Relative to baseline (week 0), except models using BCF method, a significant difference between week 4 and baseline (week 0) in 8 mg/ml was carried through week 12 and week 24 based on MI and ITT methods. BCF was the only method which did not detect a relative to baseline (week 0) difference at week 24 but effects were consistent at earlier time points.

Exhaled carbon monoxide

Between condition significant differences in exhaled carbon monoxide were most prevalent between CS and 8 mg/ml, between CS and 36 mg/ml, between 0 and 8 mg/ml and between 0 and 36 mg/ml starting at the first post-randomization visit (week 1) to the last visit in the intervention period (week 24). Discrepancies in results among MI, ITT, and BCF methods were observed but no systematic differences were found with regards to the results inferences. Notable discrepancies included a significant difference between CS and 36 mg/ml at week 1 only found in MI unadjusted model and a significant difference between 0 mg/ml and 36 mg/ml at week 8 only found in BCF unadjusted model. A significant difference between CS and 36 mg/ml at week 2 was found using both ITT and BCF methods but not MI. Significant differences between 0 mg/ml and 8 mg/ml at week 4, and between 0 mg/ml and 36 mg/ml at week 24 were observed based on MI unadjusted model and BCF unadjusted/adjusted models but not ITT. BCF did not detect the significant difference between CS and 36 mg/ml at week 24, however, it was observed using MI unadjusted/adjusted models and ITT adjusted model.

Similarly, in the comparisons relative to baseline (week 0), no systematic shifts in the inferential results were observed among the three methods while small discrepancies were noted. For 8 mg/ml, all three methods found significant differences relative to baseline (week 0) in all following weeks except week 24. At week 24, exhaled carbon monoxide did not significantly differ from baseline (week 0) based on BCF method or based on MI unadjusted model. Additionally, BCF unadjusted model did not detect a significant difference between week 20 and baseline (week 0) for 8 mg/ml. For 36 mg/ml, all weeks following baseline (week 0) showed significant differences using MI, ITT, and BCF methods except week 16 in BCF unadjusted model. Significant differences relative to baseline (week 0) in CS at weeks 4 and 12 were observed based on the ITT method and MI adjusted model, but not BCF. A significant difference between week 2 and baseline (week 0) in 0 mg/ml in both unadjusted and adjusted models across methods were observed except BCF unadjusted model. A significant difference between week 1 and baseline (week 0) for 0 mg/ml was observed based on the ITT unadjusted model and BCF method, but not MI. BCF method did not detect the significant difference between week 4 and baseline (week 0) for 0 mg/ml but this significant difference was observed for both MI adjusted model and ITT method. The difference between week 8 and baseline (week 0) in 8 mg/ml was only significant using ITT method.

Cigarettes smoked per day

Compared to unadjusted models, more significant between-condition differences were observed in adjusted models regardless the analysis method used. Most prevalent significant differences were observed between CS and 0 mg/ml, between CS and 8 mg/ml and between CS and 36 mg/ml. All significant differences found based on MI method between CS and 36 mg/ml at weeks 1, 2, 4, 8, 12 and 16 were also be able to be detected by ITT and BCF methods. Additionally, this significance was further carried through week 20 and week 24 in MI and ITT models. Significant differences between CS and 0 mg/ml at weeks 4, 8 and 16 were detected by both MI and ITT unadjusted models but not BCF. MI and ITT adjusted models further found significant differences at weeks 1, 2, 12, 20 and 24 in addition to significant differences above. BCF adjusted model only found significant differences between CS and 0 mg/ml at weeks 2, 4 and 8. ITT unadjusted/adjusted models and MI adjusted model detected significant differences between CS and 8 mg/ml at most weeks, but the difference only was observed at week 4 using MI unadjusted model. No significant differences between CS and 8 mg/ml were detected by BCF unadjusted model and BCF adjusted model only detected significances at weeks 2, 4 and 8.

In the pairwise comparisons relative to baseline (week 0), all three methods consistently detected significant differences relative to baseline (week 0) for all post-randomization time points within all conditions.

Adverse events

Detailed description of all adverse events, by number of events and by number of participants, is presented in Table S75 and Table S76. All serious adverse events were reported to be unrelated or unlikely to be related (Table S77). Table S78 presents a description of serious/severe events as well as withdrawal-related information.

Figure S1. Study design schematic by week

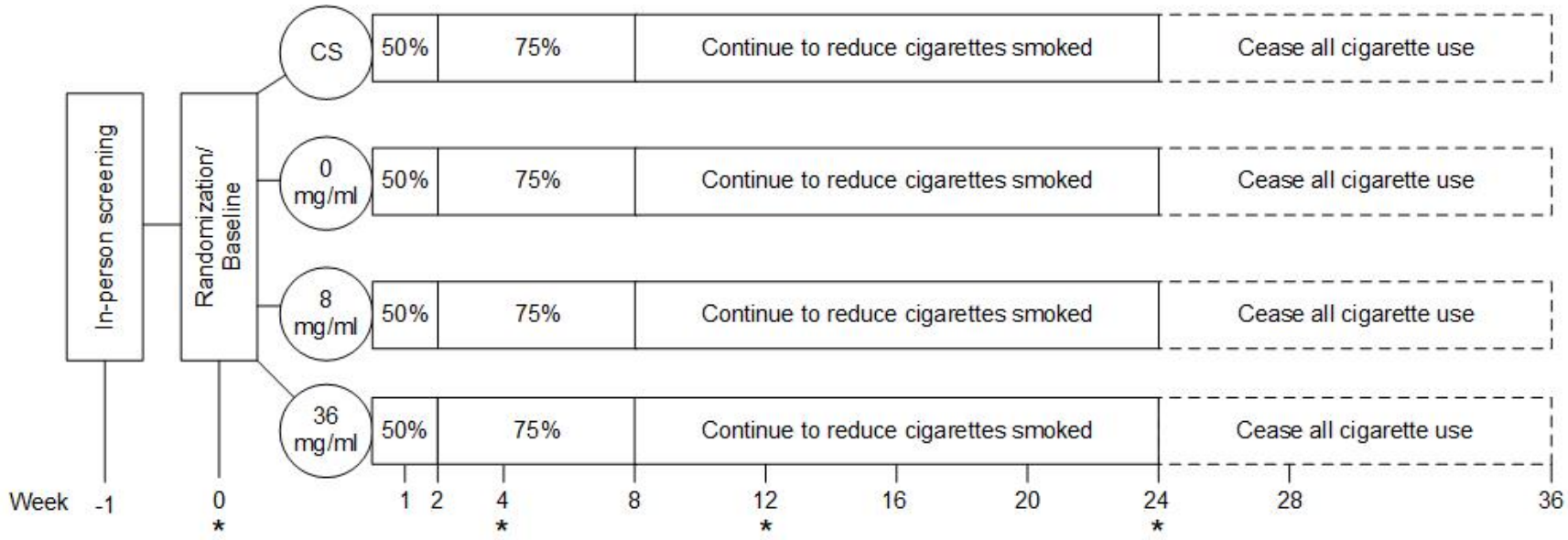

Figure S1: Study design schematic by week and condition with in-person clinic visits indicated. Cigarette smoking instructions that were active during a given week are indicated: 50% reduction (week 0-2), 75% reduction (week 3-8), continue to reduce cigarettes smoked (weeks 9-24; i.e., until the end of the intervention period), and advised to cease all cigarette use (week 25-36; follow-up period). Asterisks (*) indicate that urine, blood, and exhaled breath condensate samples were collected at that visit. The dotted line indicates the follow-up period during which participants were provided the alternate study product to which they were randomised at the week 24 visit.

Figure S2: Adjusted urinary total NNAL using multiple imputation

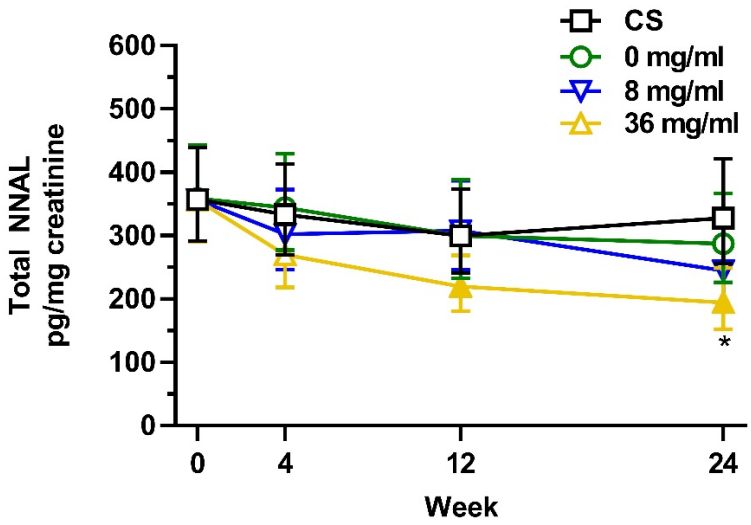

Figure S2: Urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) adjusted for creatinine. Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed). Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·017). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S3: Unadjusted and adjusted urinary total NNAL sensitivity analyses: Intent-to-treat and per-protocol

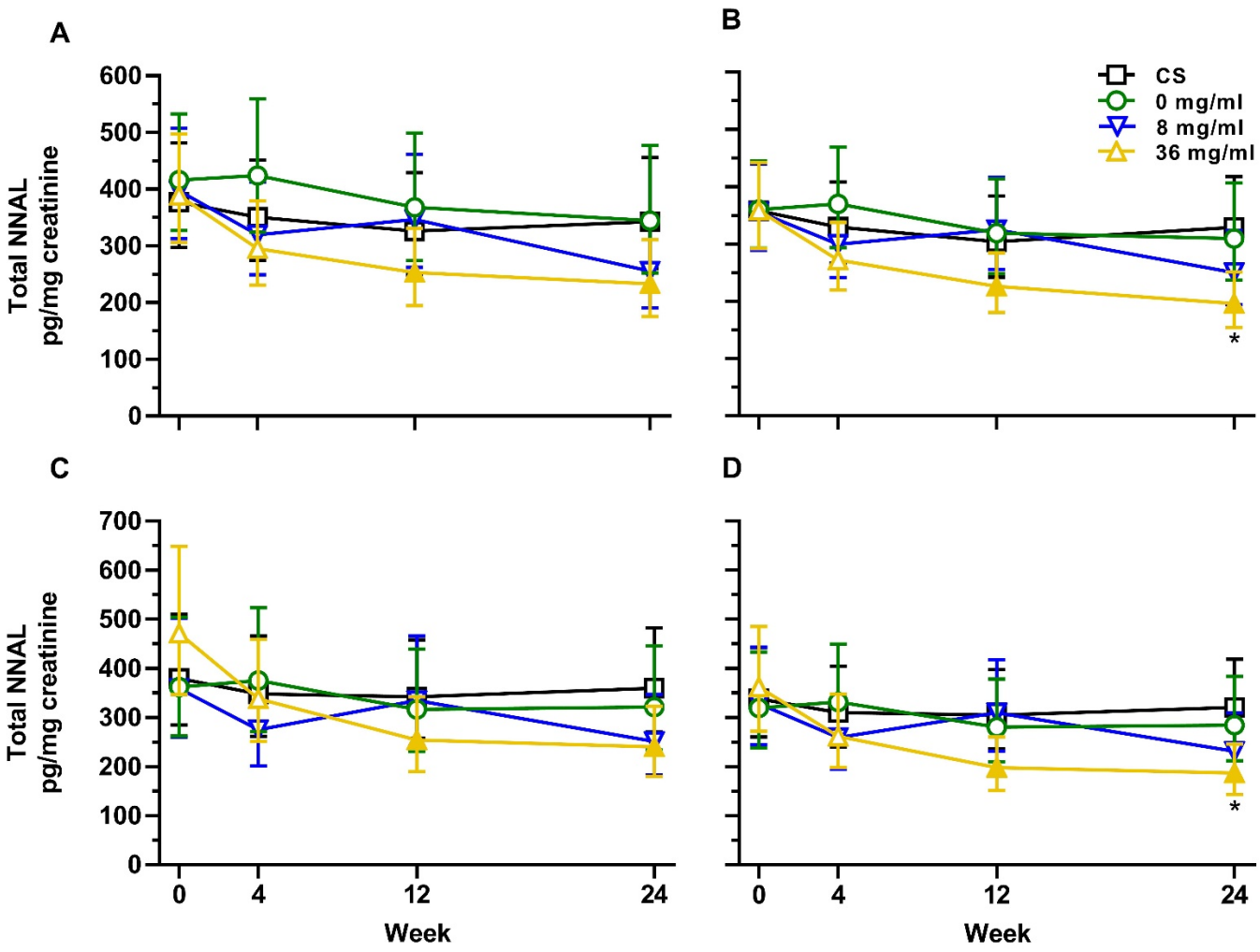

Figure S3: Urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) adjusted for creatinine. Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation. Panels A (unadjusted) and B (adjusted) represent intent-to-treat data (all available with no imputation). Panels C (unadjusted) and D (adjusted) represent per-protocol (individuals who attended and provided data at week 0 4, 12, and 24). Adjusted models included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed). Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·017). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S4. Unadjusted and adjusted urinary total NNAL sensitivity analyses: baseline-carried-forward and last-observation-carried-forward

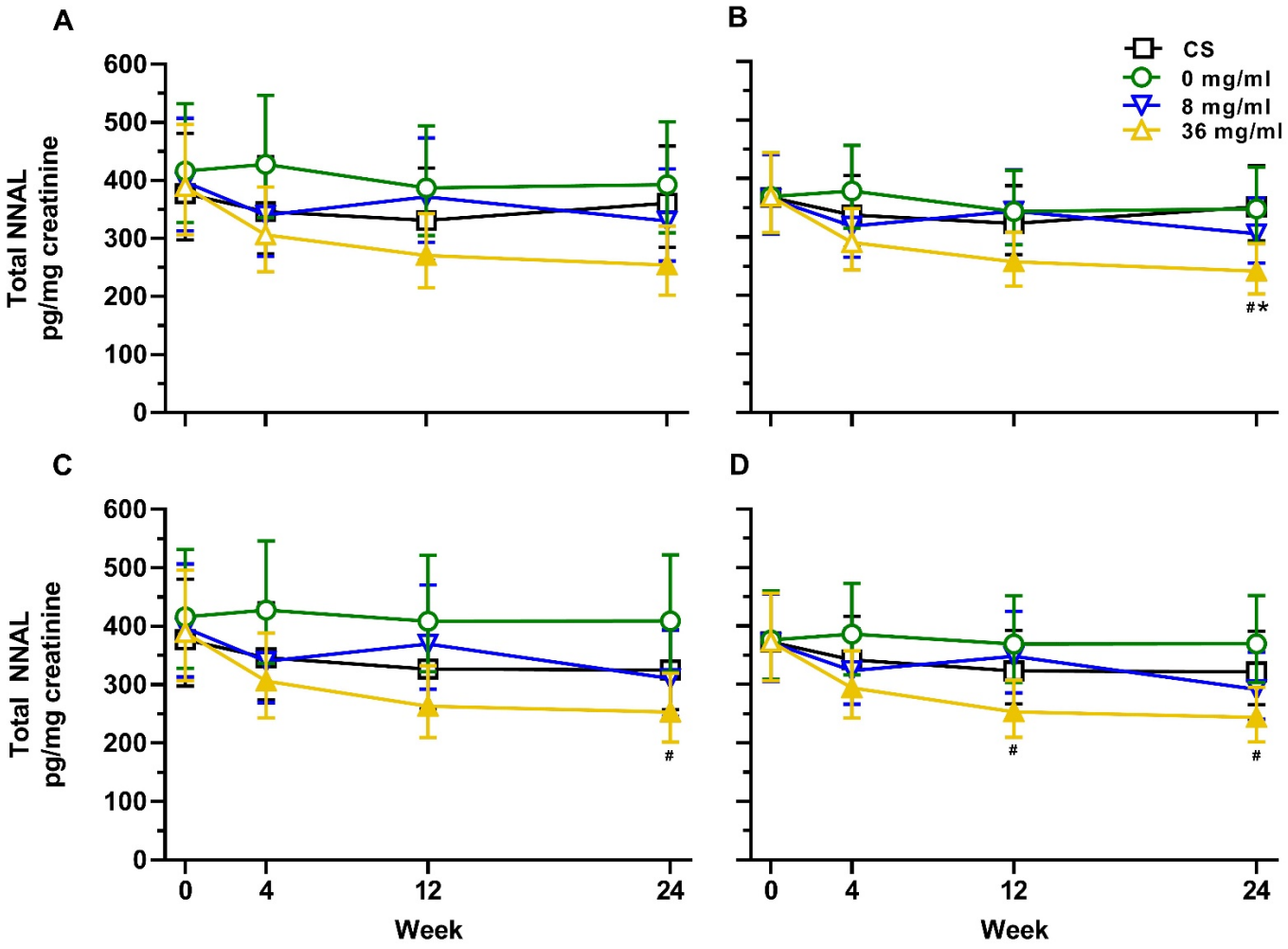

Figure S4: Urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) adjusted for creatinine. Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation. Panels A (unadjusted) and B (adjusted) represent baseline-carried-forward data (missing data replaced with week 0 data). Panels C (unadjusted) and D (adjusted) represent last-observation-carried-forward data (missing data replaced with last observation available for that participant). Adjusted models included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed). Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·017). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0.008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S5: Adjusted urinary cotinine using multiple imputation

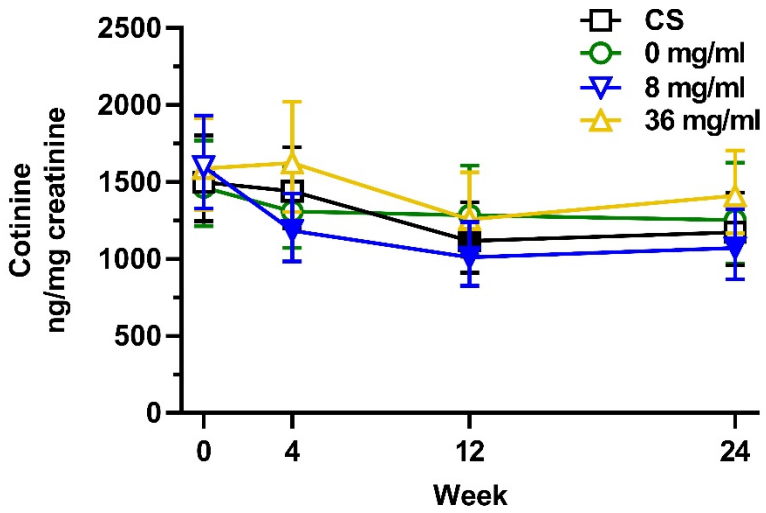

Figure S5: Urinary cotinine adjusted for creatinine. Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·017). There were no significant differences between conditions at any time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S6: Unadjusted and adjusted urinary cotinine sensitivity analyses: Intent-to-treat and per-protocol

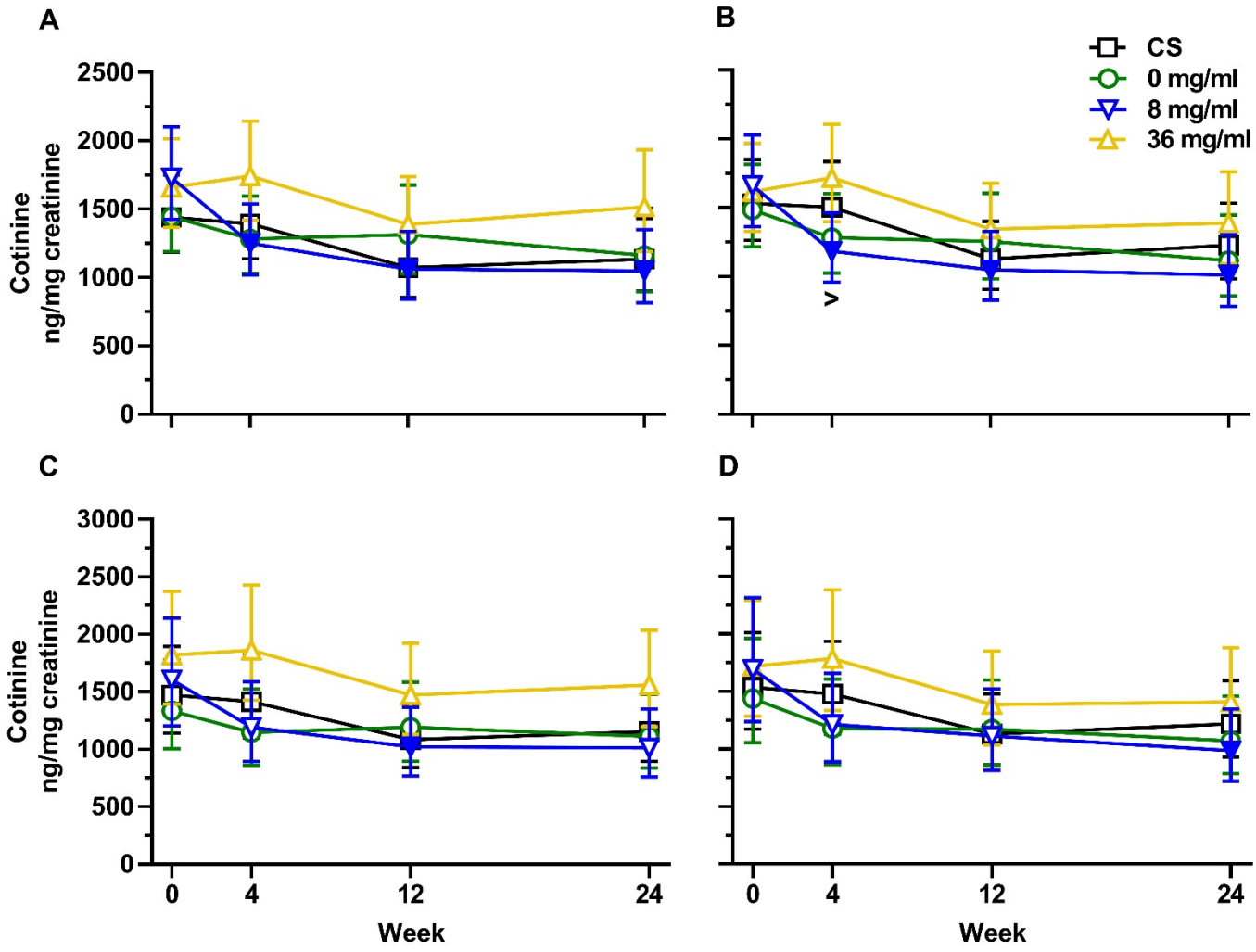

Figure S6: Urinary cotinine adjusted for creatinine. Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation. Panels A (unadjusted) and B (adjusted) represent intent-to-treat data (all available with no imputation). Panels C (unadjusted) and D (adjusted) represent per-protocol (individuals who attended and provided data at week 0 4, 12, and 24). Adjusted models included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·017). Greater-than signs (>) indicate a significant difference relative to the 36 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S7: Unadjusted and adjusted urinary cotinine sensitivity analyses: Baseline-carried-forward and last-observation carried-forward

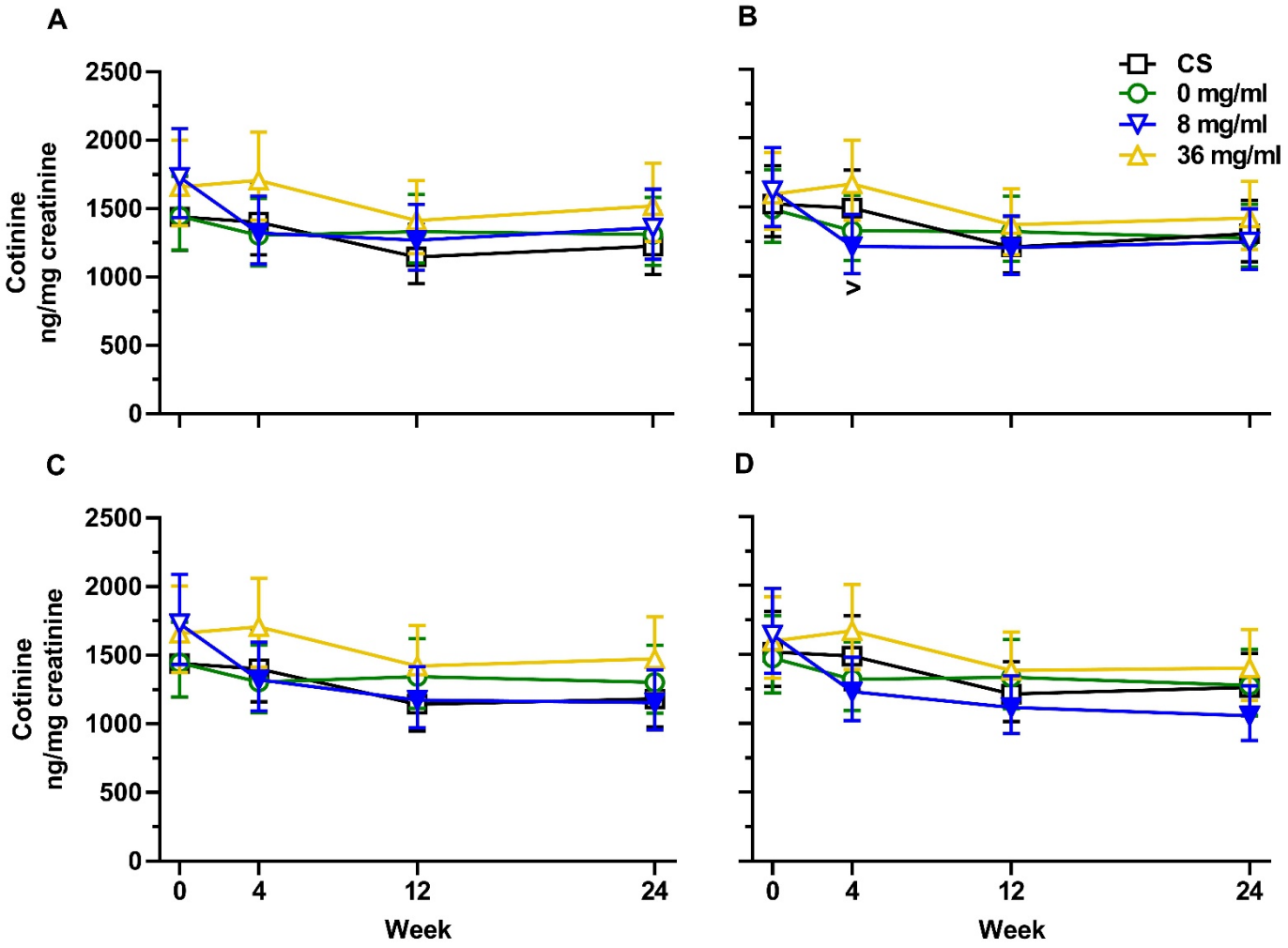

Figure S7: Urinary cotinine adjusted for creatinine. Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation. Panels A (unadjusted) and B (adjusted) represent baseline-carried-forward data (missing data replaced with week 0 data). Panels C (unadjusted) and D (adjusted) represent last-observation-carried-forward data (missing data replaced with last observation available for that participant). Adjusted models included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·017). Greater-than signs (>) indicate a significant difference relative to the 36 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S8: Adjusted exhaled carbon monoxide using multiple imputation

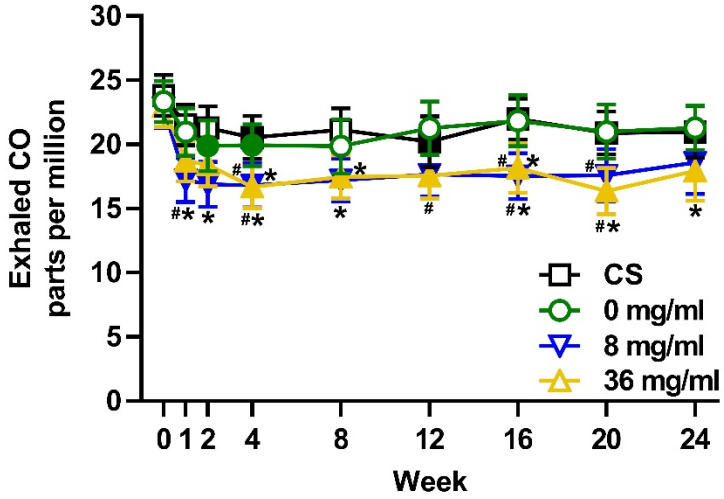

Figure S8. Exhaled carbon monoxide (CO) is presented as estimated means with 95% confidence intervals following multiple imputation. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·006). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S9: Unadjusted and adjusted exhaled carbon monoxide sensitivity analyses: Intent-to-treat and per-protocol

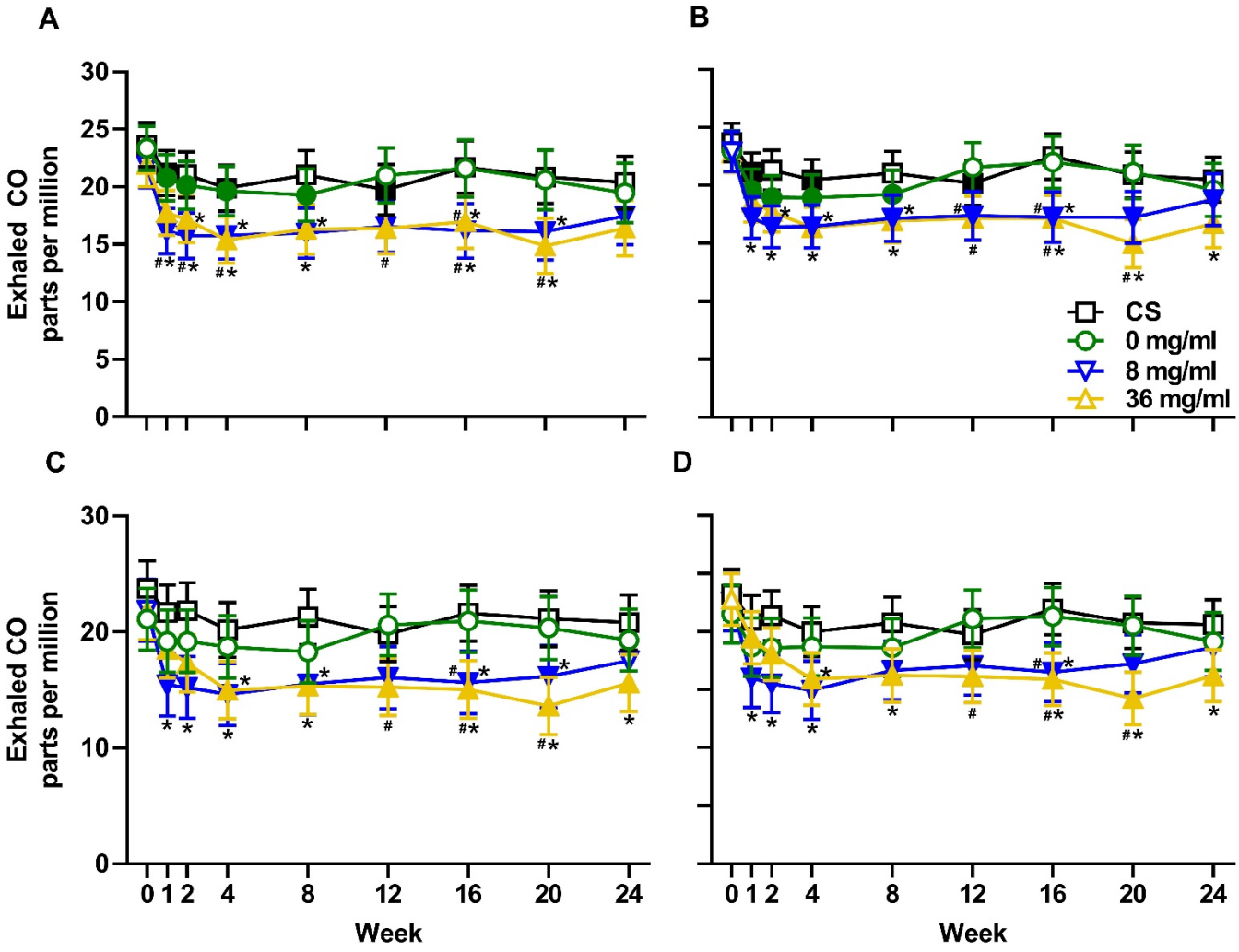

Figure S9: Exhaled carbon monoxide (CO) is presented as estimated means with 95% confidence intervals. Panels A (unadjusted) and B (adjusted) represent intent-to-treat data (all available with no imputation). Panels C (unadjusted) and D (adjusted) represent per-protocol (individuals who attended and provided data at week 0 4, 12, and 24). Adjusted models included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·006). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S10: Unadjusted and adjusted exhaled carbon monoxide sensitivity analyses: Baseline-carried-forward and last-observation-carried-forward

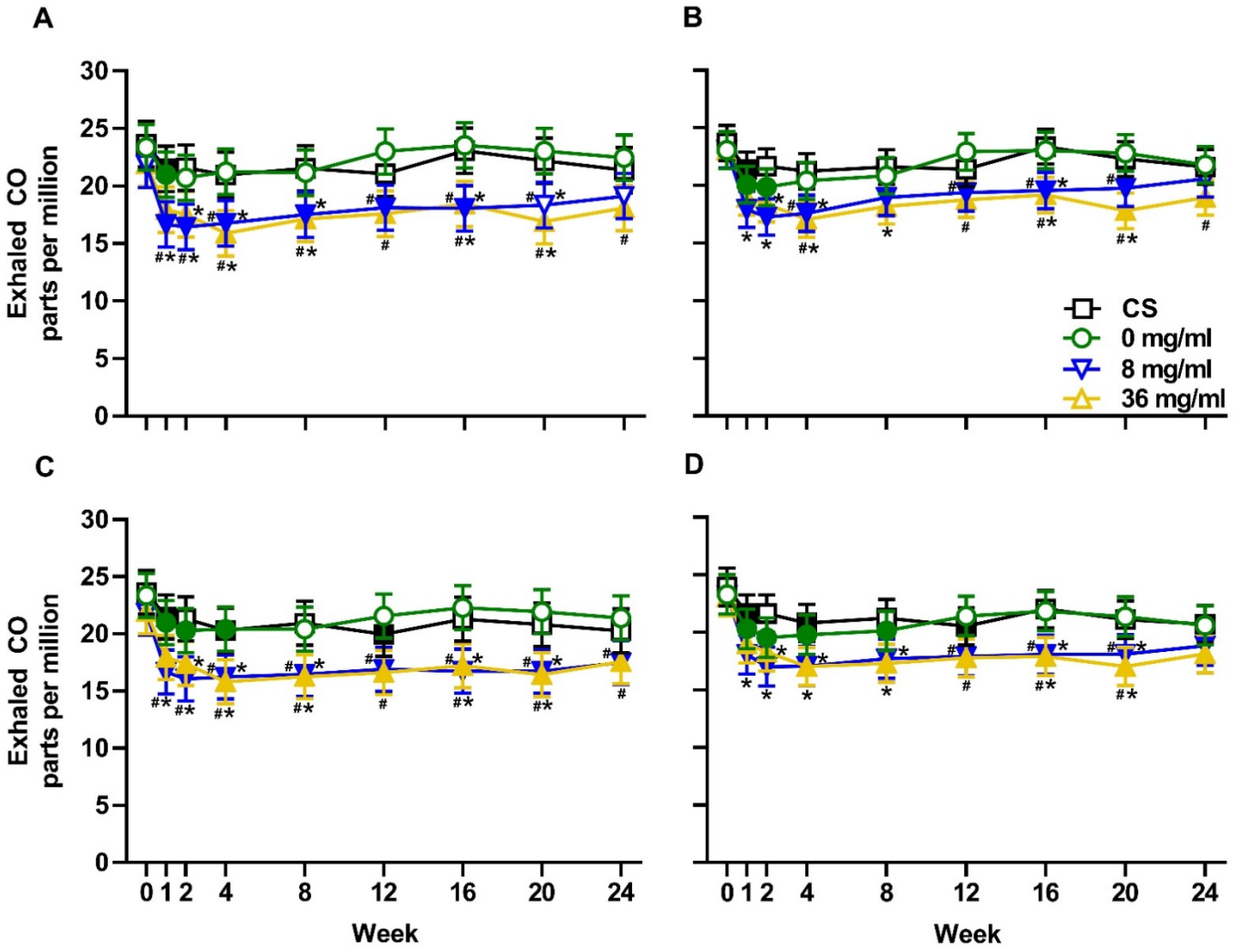

Figure S10. Exhaled carbon monoxide (CO) is presented as estimated means with 95% confidence intervals. Panels A (unadjusted) and B (adjusted) represent baseline-carried-forward data (missing data replaced with week 0 data). Panels C (unadjusted) and D (adjusted) represent last-observation-carried-forward data (missing data replaced with last observation available for that participant). Adjusted models included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·006). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S11: Adjusted cigarettes smoked per day using multiple imputation

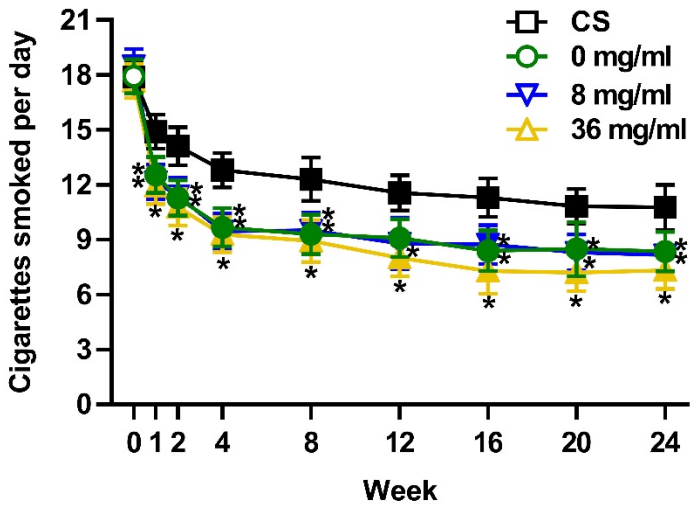

Figure S11: Cigarettes smoked per day (CPD) in the 7 days prior using a timeline-follow-back procedure is presented as estimated means with 95% confidence intervals following multiple imputation. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·006). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S12: Unadjusted and adjusted cigarettes per day sensitivity analyses: Intent-to-treat and per-protocol

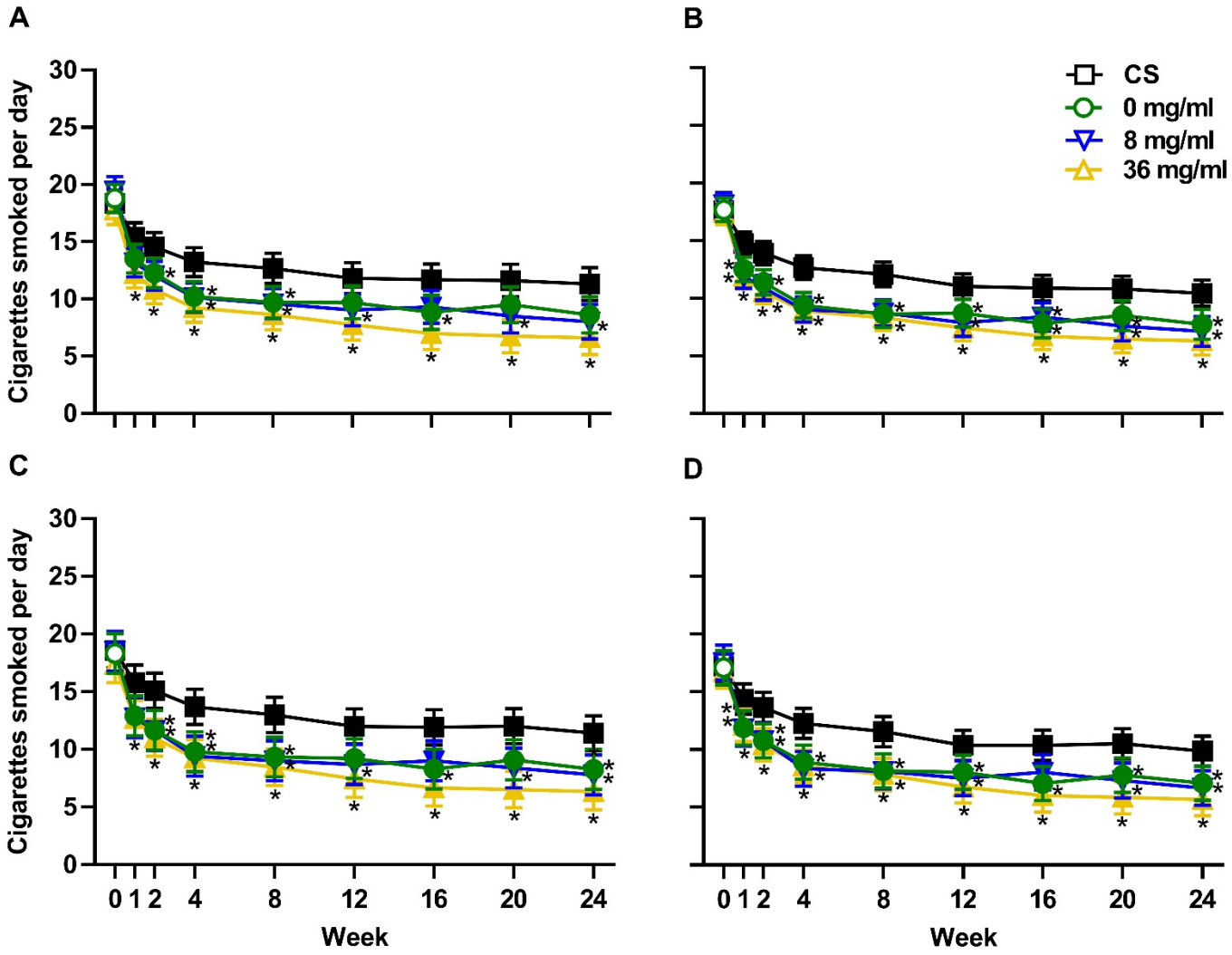

Figure S12: Cigarettes smoked per day (CPD) in the 7 days prior using a timeline-follow-back procedure is presented as estimated means with 95% confidence intervals. Panels A (unadjusted) and B (adjusted) represent intent-to-treat data (all available with no imputation). Panels C (unadjusted) and D (adjusted) represent per-protocol (individuals who attended and provided data at week 0, 4, 12, and 24). Adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·006). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S13: Unadjusted and adjusted cigarettes per day sensitivity analyses: Baseline-carried-forward and last-observation carried-forward

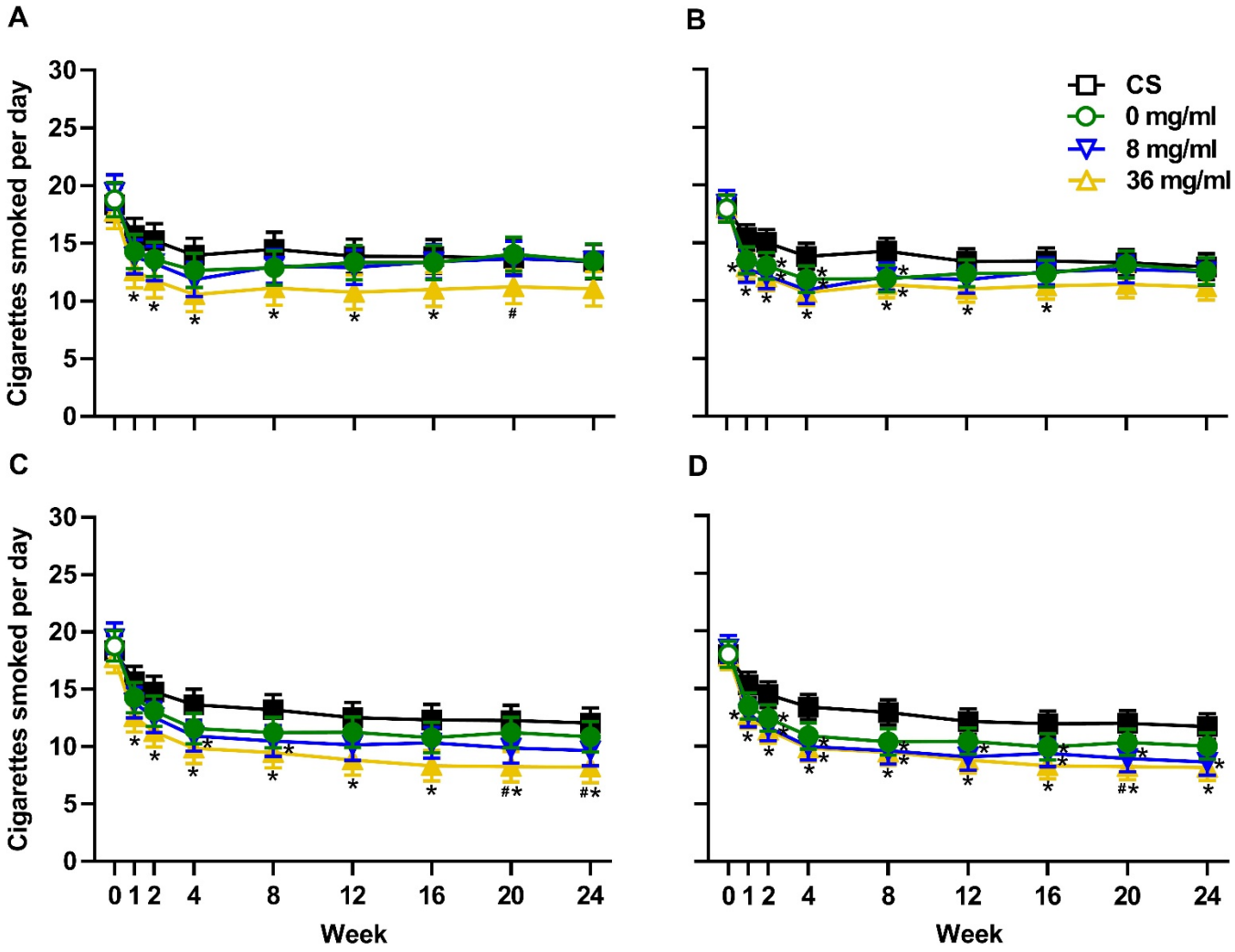

Figure S13. Cigarettes smoked per day (CPD) in the 7 days prior using a timeline-follow-back procedure is presented as estimated means with 95% confidence intervals. Panels A (unadjusted) and B (adjusted) represent baseline-carried-forward data (missing data replaced with week 0 data). Panels C (unadjusted) and D (adjusted) represent last-observation-carried-forward data (missing data replaced with last observation available for that participant). Adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·006). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Figure S14. Unadjusted study product use: intent-to-treat (missing assumed no use), intent-to-treat (only available data), per-protocol

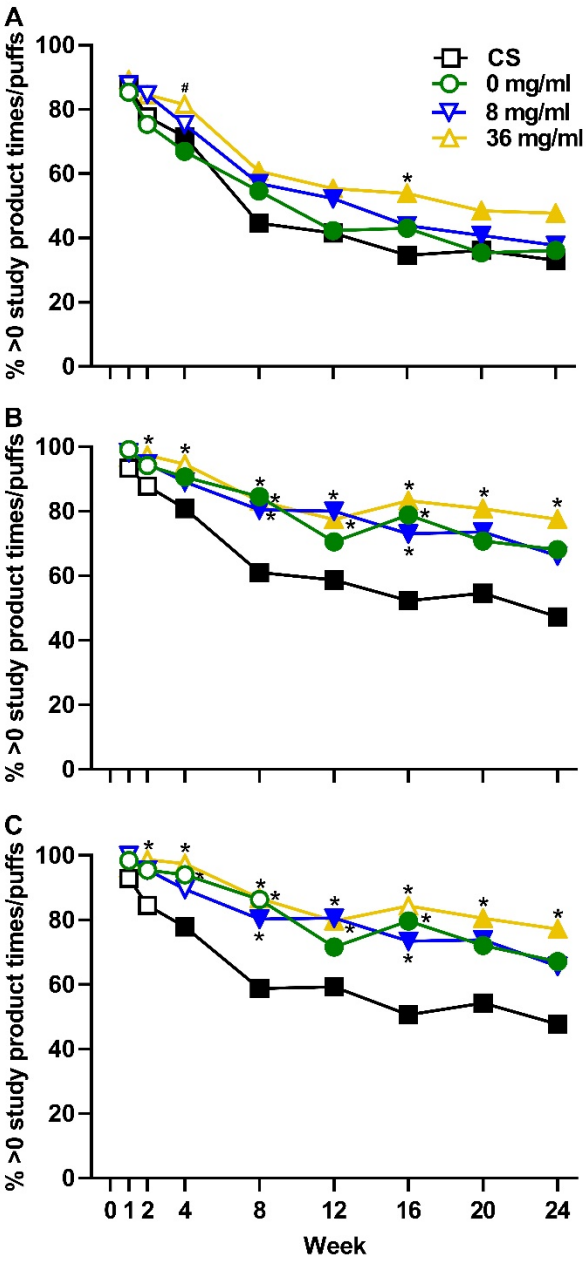

Figure S14: Study product use in the 7 days prior using a timeline-follow-back procedure is presented as percent (%) with more than 0 times/puffs reported. Panels A (intent-to-treat [ITT]; all available and missing assumed = 0 times/uses), B (ITT; all available with no imputation), and C (per-protocol; individuals who attended and provided data at week 0, 4, 12, and 24) have no adjustments for baseline covariates. Filled symbols indicate a significant difference relative to week 0 within that condition (Bonferroni correction alpha=0·007). Asterisks (*) indicate a significant difference relative to the cigarette substitute (CS) for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions). Number signs (#) indicate a significant difference relative to the 0 mg/ml condition for that condition at that time point (Bonferroni correction alpha=0·008, between all conditions).

Table S1. Detailed baseline characteristics

			Electronic Nicotine Delivery System Conditions								
	Cigarette substitute		0 mg/ml		8 mg/ml		36 mg/ml		Overall		
Sociodemographics	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**P**
Age, year	130	46·1±12·4 (21·0,65·0)	130	45·7±11·4 (21·0,64·0)	130	45·6±11·7 (23·0,65·0)	130	47·4±11·1 (22·0,65·0)	520	46·2±11·6 (21·0,65·0)	0·58
Sex, %	130		130		130		130		520		
Male	51	39·2	50	38·5	50	38·5	63	48·5	214	41·2	0·28
Female	79	60·8	80	61·5	80	61·5	67	51·5	306	58·8	
Race/Ethnicity, %	130		130		130		130		520		0·94
Caucasian/White NH	83	63·9	92	70·8	87	66·9	88	67·7	350	67·3	
African American/Black NH	39	30·0	33	25·4	37	28·5	36	27·7	145	27·9	
Other	8	6·2	5	3·9	6	4·6	6	4·6	25	4·8	
Hispanic, %	130		130		130		130		130		0·19
Yes	1	0·8	0	0·0	3	2·3	4	3·1	8	1·5	
Education, %	130		130		130		130		520		0·72
Less than 12th grade/No diploma	12	9·2	19	14·6	13	10·0	12	9·2	56	10·8	
High school graduate/GED	42	32·3	39	30·0	34	26·2	39	30·0	154	29·6	
Some college/No degree	38	29·2	44	33·9	47	36·2	41	31·5	170	32·7	
Associate's degree	20	15·4	17	13·1	15	11·5	17	13·1	69	13·3	
Bachelor's degree or higher	18	13·9	11	8·5	21	16·2	21	16·2	71	13·7	
Employment status, %	130		129		129		130		518		0·34
Full-time	54	41·5	50	38·8	66	51·2	57	43·9	227	43·8	
Part-time	18	13·9	18	14·0	26	20·2	18	13·9	80	15·4	
Retired	10	7·7	11	8·5	8	6·2	11	8·5	40	7·7	
Military	0	0·0	0	0·0	1	0·8	0	0·0	1	0·2	
Student	2	1·5	1	0·8	2	1·6	2	1·5	7	1·4	
Unemployed	46	35·4	49	38·0	26	20·2	42	32·3	163	31·5	
Total household income, %	128		127		125		13-		510		0·87
Less than $10,000	26	20·3	32	25·2	23	18·4	27	20·8	108	21·2	

$10,000-$39,999	51	39·8	48	37·8	51	40·8	43	33·1	193	37·8	
$40,000-$69,999	27	21·1	20	15·8	24	19·2	30	23·1	101	19·8	
$70,000-$99,999	16	12·5	18	14·2	14	11·2	19	14·6	67	13·1	
$100,000 or more	8	6·3	9	7·1	13	10·4	11	8·5	41	8·0	
Marital Status, %	129		129		130		130		518		0·34
Married	32	24·8	37	28·7	44	33·9	40	30·8	153	29·5	
Widowed	10	7·8	4	3·1	4	3·1	3	2·3	21	4·1	
Divorced	21	16·3	27	20·9	20	15·4	20	15·4	88	17·0	
Separated	14	10·9	8	6·2	4	3·1	9	6·9	35	6·8	
Never married	28	21·7	30	23·3	38	29·2	36	27·7	132	25·5	
Living with a partner	19	14·7	17	13·2	16	12·3	20	15·4	72	13·9	
Member of an unmarried couple (not living together)	5	3·9	6	4·7	4	3·1	2	1·5	17	3·3	
Baseline tobacco use characteristics	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**P**
Cigarettes smoked per day (CPD)											
Week -1	130	19·9±7·8 (10·0,40·0)	130	20·5±9·3 (10·0,60·0)	130	20·2±11·2 (10·0,100·0)	130	19·5±7·1 (10·0,46·0)	520	20·0±8·9 (10·0,100·0)	0·85
Week 0	130	18·4±7·1 (9·3,45·0)	130	18·8±8·3 (8·7,64·1)	130	19·4±8·7 (8·1,60·7)	130	17·8±6·5 (7·9,47·3)	520	18·6±7·7 (7·9,64·1)	0·35
Years smoking this number of CPD at week -1	130	15·8±13·2 (0·02,50·0)	130	15·7±13·0 (0·08,50·0)	130	16·4±13·0 (0·08,46·0)	130	17·9±13·3 (0·17,50·0)	520	16·5±13·1 (0·02,50·0)	0·49
Age of cigarette smoking initiation at week -1	130	16·6±4·1 (6·0,33·0)	127	16·5±4·9 (6·0,42·0)	127	17·7±4·8 (9·0,35·0)	130	17·0±3·5 (8·0,30·0)	514	17·0±4·4 (6·0,42·0)	0·12
PSCDI score at Week 0	127	13·4±3·0 (5·0,19·0)	120	13·7±2·7 (6·0,20·0)	121	13·2±3·0 (7·0,19·0)	127	13·2±3·2 (7·0,20·0)	495	13·4±3·0 (5·0,20·0)	0·46
Menthol cigarette smokers, %	130		130		130		130		520		0·44
Yes	87	66·9	88	67·7	81	62·3	77	59·2	333	64·0	
Use of other tobacco product(s) in past 30 days at week -1, %	130		130		130		130		520		0·42
Yes	4	3·1	9	6·9	10	7·7	8	6·2	31	6·0	
Baseline psychosocial/health characteristics	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**P**
AUDIT-C score at week -1	128	2·0±2·0 (0·0,10·0)	129	2·3±2·4 (0·0,11·0)	129	2·7±2·5 (0·0,10·0)	126	2·3±2·4 (0·0,10·0)	512	2·3±2·4 (0·0,11·0)	0·08

Environmental smoke score at week 0, %	128		128		125		129		510		0·60
Little or no exposure	36	27·7	32	25·0	26	20·8	36	27·9	130	25·5	
Moderate exposure	32	25·0	25	19·5	33	26·4	32	24·8	122	23·9	
High exposure	60	46·9	71	55·5	66	52·8	61	47·3	258	50·6	
Kessler K6 score at week 0	126	5·0±4·5 (0·0,21·0)	128	4·8±4·0 (0·0,17·0)	124	5·0±3·9 (0·0,20·0)	128	4·9±4·2 (0·0,17·0)	506	4·9±4·2 (0·0,21·0)	0·99
Perceived Stress Scale score at week 0	126	19·8±4·5 (0·0,32·0)	124	20·0±4·3 (0·0,34·0)	125	19·3±3·5 (4·0,35·0)	130	20·3±4·0 (9·0,35·0)	505	19·9±4·1 (0·0,35·0)	0·23
CES-D score at week 0	115	13·2±10·2 (0·0,39·0)	118	12·5±9·6 (0·0,48·0)	120	11·9±9·1 (0·0,47·0)	121	11·8±10·3 (0·0,44·0)	474	12·3±9·8 (0·0,48·0)	0·67
Partial INTERHEART non-laboratory score at week 0	125	10·0±3·3 (1·0,18·0)	124	9·6±3·5 (0·0,20·0)	122	10·2±3·2 (2·0,17·0)	123	10·1±3·5 (3·0,18·0)	494	10·0±3·4 (0·0,20·0)	0·48
Clinical COPD Questionnaire score at week 0	127	1·2±0·9 (0·0,5·0)	123	1·2±0·8 (0·0,3·7)	128	1·2±0·8 (0·0,3·4)	128	1·3±1·0 (0·0,5·3)	506	1·2±0·9 (0·0,5·3)	0·74
Baseline physiological measures^	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**N**	**Mean±SD (Min., Max.)**	**P**
Urinary total NNAL, pg/mg creatinine											
Median (IQR)	130	441·4 (683·2)	130	499·8 (612·2)	130	420·0 (835·6)	130	544·4 (825·3)	520	473·2 (710·6)	0·79*
Geometric mean (95% CI)	130	404·2 (330·5, 494·4)	130	440·7 (366·4, 530·0)	130	425·0 (347·3, 520·1)	130	432·7 (339·3, 551·8)	520	425·4 (383·6, 471·8)	
Urinary cotinine, ng/mg creatinine											
Median (IQR)	130	1641·2 (2018·3)	130	1593·2 (1564·1)	130	1734·0 (2057·5)	130	1871·5 (2137·7)	520	1662·5 (1908·6)	0·24*
Geometric mean (95% CI)	130	1441·6 (1227·9, 1692·4)	130	1444·5 (1241·5, 1680·8)	130	1729·5 (1494·0, 2002·2)	130	1658·7 (1411·2, 1949·7)	520	1563·4 (1447·4, 1688·7)	
Waist circumference, cm	130	103·3±18·7 (68·6, 172·7)	129	102·4±20·0 (63·5, 154·9)	129	102·2±17·2 (68·6, 144·8)	130	103·5±16·8 (66·0, 151·1)	518	102·8±18·2 (63·5, 172·7)	0·91
Hip circumference, cm	130	110·6±15·3 (77·5, 154·9)	129	109·4±16·6 (78·7, 160·0)	129	109·2±14·1 (71·1, 148·6)	130	110·2±14·9 (81·3, 162·6)	518	109·9±15·2 (71·1, 162·6)	0·87
Height, cm	130	170·0±9·4 (146·1, 193·0)	130	169·2±9·4 (141·0, 190·5)	129	170·4±9·0 (143·5, 188·0)	130	170·7±9·3 (152·4, 190·5)	519	170·1±9·3 (141·0, 193·0)	0·60

Weight, kg	130	87·1±22·8 (47·5, 164·0)	130	85·0±26·1 (39·3, 167·4)	130	84·8±20·0 (47·2, 139·1)	130	87·3±22·9 (43·9, 154·6)	520	86·0±23·0 (39·3, 167·4)	0·72
BMI, kg/m^2	130	30·3±7·2 (17·5, 52·8)	130	29·7±8·1 (14·7, 55·8)	130	29·5±6·6 (16·6, 50·7)	130	30·2±7·4 (17·3, 53·8)	519	30·0±7·3 (14·7, 55·8)	0·80
FEV1, cm^3	130	2680·2±867·8 (890·0, 5710·0)	130	2641·1±862·2 (540·0, 5020·0)	128	2713·9±859·3 (930·0,4720·0)	130	2623·2±835·7 (900·0, 4760·0)	518	2664·4±854·6 (540·0,5710·0)	0·83
FVC, cm^3	130	3396·5±1056·6 (1400·0, 6920·0)	130	3397·8±989·3 (540·0, 6330·0)	128	3443·1±1008·9 (1330·0, 5980·0)	130	3353·3±968·8 (1320·0, 6190·0)	518	3397·5±1004·0 (540·0,6920·0)	0·92
CO, parts per million	130	23·6±12·5 (5·0,92·0)	130	23·4±12·2 (4·0,74·0)	130	21·8±9·8 (8·0,53·0)	130	21·9±10·5 (2·0,68·0)	520	22·7±11·3 (2·0,92·0)	0·44
Pulse, beats per minute	130	81·4±13·0 (50·0,113·0)	130	83·0±14·1 (50·0,121·0)	130	80·9±12·4 (49·0,131·0)	129	81·9±12·8 (53·0,114·0)	519	81·8±13·1 (49·0,131·0)	0·58
Systolic blood pressure, mmHg	130	125·3±14·0 (94·0,159·0)	130	124·3±13·8 (91·0,165·0)	130	124·6±14·5 (95·0,172·0)	129	127·1±15·5 (88·0,186·0)	519	125·3±14·5 (88·0,186·0)	0·43
Diastolic blood pressure, mmHg	130	78·6±9·9 (58·0,106·0)	130	79·6±9·7 (57·0,105·0)	130	78·2±10·1 (59·0,116·0)	129	80·3±9·8 (59·0,102·0)	519	79·2±9·9 (57·0,116·0)	0·32

Note: SD, standard deviation; Min., minimum; Max., maximum; cm, centimeter; kg, kilogram; GED, general education diploma; CPD, cigarettes per day; PSCDI, Penn State Cigarette Dependence Index; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; CES-D, Center for Epidemiologic Studies Depression Scale; COPD, Chronic Obstructive Pulmonary Disease; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; BMI, body mass index; FEV1, Forced expiratory volume in one second; FVC, forced vital capacity; CO, carbon monoxide; CI, confidence interval.

^All baseline physiological measures obtained at week 0.

***** Based on Kruskal-Wallis test.

Table S2. Detailed baseline characteristics by site

	VCU (N=200)		PSU (N=320)		
Sociodemographics	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
Age, year	200	46·8±12·3 (21·0, 65·0)	320	45·9±11·2 (21·0, 65·0)	0·36
Sex, %	200		320		0·0006
Male	101	50·5	113	35·3	
Female	99	49·5	207	64·7	
Race/Ethnicity, %	200		320		<0·0001
Caucasian/White NH	65	32·5	285	89·1	
African American/Black NH	126	63·0	19	5·9	
Other	9	4·5	16	5·0	
Hispanic, %	200		320		0·03
Yes	0	0·0	8	2·5	
Education, %	200		320		0·10
Less than 12^{th} grade/No diploma	30	15·0	26	8·1	
High school graduate/GED	57	28·5	97	30·3	
Some college/No degree	67	33·5	103	32·2	
Associate's degree	24	12·0	45	14·1	
Bachelor's degree or higher	22	11·0	49	15·3	
Employment status, %	119		319		<0·0001
Full-time	62	31·2	165	51·7	
Part-time	39	19·6	41	12·9	
Retired	16	8·0	24	7·5	
Military	1	0·5	0	0·0	
Student	4	2·0	3	0·9	
Unemployed	77	38·7	4	27·0	
Total household income, %	195		315		<0·0001
Less than $10,000	79	40·5	29	9·2	
$10,000-$39,999	78	40·0	115	36·5	
$40,000-$69,999	19	9·7	82	26·0	

$70,000-$99,999	9	4·6	58	18·4	
$100,000 or more	10	5·1	31	9·8	
Marital Status, %	199		319		<0·0001
Married	27	13·6	126	39·5	
Widowed	11	5·5	10	3·1	
Divorced	31	15·6	57	17·9	
Separated	19	9·6	16	5·0	
Never married	76	38·2	56	17·6	
Living with a partner	21	10·6	51	16·0	
Member of an unmarried couple (not living together)	14	7·0	3	0·9	
Baseline tobacco use characteristics	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
Cigarettes per day (CPD)					
Week -1	200	19·6±8·3 (10·0, 60·0)	320	20·3±9·3 (10·0, 100·0)	0·41
Week 0	200	17·9±6·8 (7·9, 50·3)	320	19·1±8·2 (9·4, 64·1)	0·07
Years smoking this number of CPD at week -1	200	14·4±12·2 (0·17, 46·0)	320	17·8±13·5 (0·02, 50·0)	0·005
Age of cigarette smoking initiation at week -1	196	17·2±4·8 (6·0, 42·0)	318	16·8±4·1 (7·0, 35·0)	0·35
PSCDI score at week 0	192	13·6±3·2 (5·0, 20·0)	303	13·3±2·8 (7·0, 20·0)	0·36
Menthol cigarette smokers, %	200		320		<0·0001
Yes	155	77·5	178	55·6	
Use of other tobacco product(s) in past 30 days at week -1, %	200		320		
Yes	24	12·0	7	2·2	<0·0001
Baseline psychosocial//health characteristics	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
AUDIT-C score at week -1	197	2·2±2·4 (0·0, 10·0)	315	2·4±2·3 (0·0, 11·0)	0·35
Environmental smoke score at week 0, %	200		310		0·001
High exposure	37	18·5	93	30·0	
Moderate exposure	42	21·0	80	25·8	
Little or no exposure	121	60·5	137	44·2	

Kessler K6 score at week 0	194	4·6±3·9 (0·0, 16·0)	312	5·1±4·3 (0·0, 21·0)	0·26
Perceived Stress Scale score at week 0	192	19·8±4·3 (0·0, 35·0)	313	19·9±4·0 (0·0, 35·0)	0·88
CES-D Score at week 0	181	12·2±8·9 (0·0, 39·0)	293	12·4±10·3 (0·0, 48·0)	0·84
Partial INTERHEART non-laboratory score at week 0	187	9·8±3·4 (0·0, 18·0)	307	10·0±3·3 (2·0, 20·0)	0·49
Clinical COPD Questionnaire score at week 0	194	1·2±0·9 (0·0, 5·3)	312	1·2±0·9 (0·0, 5·0)	0·38
Baseline physiological measures^	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
Urine total NNAL, pg/mg creatinine					
Median (IQR) (Min., Max.)	200	396·5 (554·7) (0·9, 10680·6)	320	609·6 (863·8) (0·4, 10985·0)	0·0002*
Geometric mean (95% CI)	200	346·2 (296·0, 404·9)	320	483·9 (422·7, 554·1)	..
Urine cotinine, ng/mg creatinine					
Median (IQR) (Min., Max.)	200	1610·7 (1513·0) (69·7, 8489·9)	320	1732·3 (2163·0) (56·1, 11980·8)	0·19*
Geometric mean (95% CI)	200	1485·5 (1328·9, 1660·5)	320	1614·1 (1454·0, 1791·9)	..
Waist circumference, cm	200	101·1±17·7 (64·8, 154·9)	318	103·9±18·4 (63·5, 172·7)	0·08
Hip circumference, cm	200	106·4±15·5 (71·1, 151·1)	318	112·0±14·6 (81·3, 162·6)	<0·0001
Height, cm	200	172·0±9·3 (144·8, 193·0)	319	168·9±9·0 (141·0, 190·5)	0·0002
Weight, kg	200	86·9±23·3 (45·3, 167·4)	320	85·5±22·8 (39·3, 151·7)	0·50
BMI, kg/m^2	200	29·6±7·4 (18·2, 53·8)	319	30·2±7·3 (14·7, 55·8)	0·39
FEV1, cm^3	199	2617·4±939·5 (540·0, 5710·0)	319	2693·7±797·2 (890·0, 4910·0)	0·34
FVC, cm^3	199	3344·1±1131·5 (540·0, 6920·0)	319	3430·8±915·8 (1390·0, 6530·0)	0·36

Exhaled CO, parts per million	200	24·5±13·4 (7·0, 92·0)	320	21·6±9·7 (2·0, 78·0)	0·01
Pulse, beats per minute	200	80·9±13·5 (49·0, 114·0)	319	82·3±12·7 (50·0, 131·0)	0·22
Systolic blood pressure, mmHg	200	127·0±14·0 (99·0, 186·0)	319	124·3±14·7 (88·0, 162·0)	0·03
Diastolic blood pressure, mmHg	200	80·7±10·1 (58·0, 116·0)	319	78·2±9·6 (57·0, 106·0)	0·01

Abbreviations: SD, standard deviation; Min., minimum; Max., maximum; cm, centimeter; kg, kilogram; GED, general education diploma; CPD, cigarettes per day; PSCDI, Penn State Cigarette Dependence Index; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; CES-D, Center for Epidemiologic Studies Depression Scale; COPD, Chronic Obstructive Pulmonary Disease; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; BMI, body mass index; FEV1, Forced expiratory volume in one second; FVC, forced vital capacity; CO, carbon monoxide; CI, confidence interval.

^All baseline physiological measures obtained at week 0.

* Based on Wilcoxon-Mann-Whitney test.

Table S3. Detailed baseline characteristics by retention status

	Week 0-24 Complete (N=332)		Week 0-24 Incomplete (N=188)		
Sociodemographics	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
Age, year	332	47·7±11·3 (21·0, 65·0)	188	43·6±11·8 (21·0, 64·0)	0·0001
Sex, %	332		188		0·95
Male	137	41·3	77	41·0	
Female	195	58·7	111	59·0	
Race/Ethnicity, %	332		188		0·52
Caucasian/White NH	221	66·6	129	68·6	
African American/Black NH	97	29·2	48	25·5	
Other	14	4·2	11	5·9	
Hispanic, %	332		188		0·72
Yes	6	1·8	2	1·1	
Education, %	332		188		0·03
Less than 12th grade/No diploma	34	10·2	22	11·7	
High school graduate/GED	90	27·1	64	34·0	
Some college/No degree	106	31·9	64	34·0	
Associate's degree	45	13·6	24	12·8	
Bachelor's degree or higher	57	17·2	14	7·5	
Employment status, %	332		186		0·08
Full-time	146	44·0	81	43·6	
Part-time	50	15·1	30	16·1	
Retired	33	9·9	7	3·8	
Military	1	0·3	0	0·0	
Student	6	1·8	1	0·5	
Unemployed	96	28·9	67	36·0	
Total household income, %	326		184		0·15
Less than $10,000	60	18·4	48	26·1	
$10,000-$39,999	132	40·5	61	33·2	
$40,000-$69,999	65	19·9	36	19·6	

$70,000-$99,999	46	14·1	21	11·4	
$100,000 or more	23	7·1	18	9·8	
Marital Status, %	331		187		0·38
Married	99	29·9	54	28·9	
Widowed	15	4·5	6	3·2	
Divorced	63	19·0	25	13·4	
Separated	20	6·0	15	8·0	
Never married	77	23·3	55	29·4	
Living with a partner	48	14·5	24	12·8	
Member of an unmarried couple (not living together)	9	2·7	8	4·3	
Baseline tobacco use characteristics	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
Cigarettes per day (CPD)					
Week -1	332	19·5±9·0 (10·0, 100·0)	188	20·9±8·8 (10·0, 60·0)	0·09
Week 0	332	18·1±7·1 (7·9, 50·9)	188	19·5±8·7 (8·7, 64·1)	0·05
Years smoking this number of CPD at week -1	332	17·6±13·5 (0·17, 50·0)	188	14·5±12·3 (0·02, 50·0)	0·01
Age of cigarette smoking initiation at week -1	328	17·4±4·7 (6·0, 42·0)	186	16·3±3·7 (6·0, 35·0)	0·003
PSCDI score at week 0	317	13·2±3·1 (5·0, 20·0)	178	13·8±2·7 (7·0, 20·0)	0·01
Menthol cigarette smoker, %	332		188		0·62
Yes	210	63·3	123	65·4	
Use of other tobacco product(s) in past 30 days at week -1, %	332		188		
Yes	20	6·0	11	5·9	0·94
Baseline psychosocial//health characteristics	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
AUDIT-C score at week -1	326	2·4±2·4 (0·0, 11·0)	186	2·2±2·3 (0·0, 10·0)	0·46
Environmental smoke score at week 0, %	327		183		0·08
High exposure	94	28·8	36	19·7	
Moderate exposure	74	22·6	48	26·2	
Little or no exposure	159	48·6	99	54·1	

Kessler K6 score at week o	324	4·8±4·1 (0·0, 21·0)	182	5·1±4·3 (0·0, 20·0)	0·35
Perceived Stress Scale score at week 0	322	19·7±4·0 (0·0, 35·0)	183	20·2±4·2 (0·0, 35·0)	0·21
CES-D Score at week 0	305	12·3±9·7 (0·0, 44·0)	169	12·5±10·0 (0·0, 48·0)	0·85
Partial INTERHEART non-laboratory score at week 0	312	9·8±3·3 (0·0, 18·0)	182	10·3±3·5 (2·0, 20·0)	0·08
Clinical COPD Questionnaire score at week 0	324	1·2±0·9 (0·0, 5·0)	182	1·3±0·9 (0·0, 5·3)	0·48
Baseline physiological measures^	N	Mean±SD (Min., Max.)	N	Mean±SD (Min., Max.)	P
Urine total NNAL, pg/mg creatinine					
Median (IQR) (Min., Max.)	332	448·3 (714·1) (1·0, 10680·6)	188	568·5 (728·1) (0·4, 10985·0)	0·16*
Geometric mean (95% CI)	332	408·6 (359·2, 464·9)	188	456·9 (383·8, 543·8)	..
Urine cotinine, ng/mg creatinine					
Median (IQR) (Min., Max.)	332	1683·2 (1895·0) (56·1, 11980·8)	188	1662·1 (1925·0) (64·1, 11459·2)	0·57*
Geometric mean (95% CI)	332	1546·7 (1406·0, 1701·5)	188	1593·3 (1396·4, 1817·9)	..
Waist circumference, cm	332	102·7±17·7 (63·5, 172·7)	186	103·1±19·0 (66·0, 154·9)	0·83
Hip circumference, cm	332	109·7±14·7 (71·1, 157·5)	186	110·1±16·1 (77·5, 162·6)	0·77
Height, cm	332	169·7±9·0 (141·0, 190·5)	187	170·8±9·7 (143·5, 193·0)	0·19
Weight, kg	332	85·2±21·1 (39·3, 151·7)	188	87·6±25·9 (43·9, 167·4)	0·29
BMI, kg/m^2	332	29·8±6·9 (14·7, 52·8)	187	30·2±8·0 (16·6, 55·9)	0·59
FEV1, cm^3	331	2619·1±816·1 (540·0, 4760·0)	187	2744·7±915·6 (900·0, 5710·0)	0·11
FVC, cm^3	331	3327·7±949·9 (540·0, 6530·0)	187	3521·0±1084·9 (1320·0, 6920·0)	0·04

Exhaled CO, parts per million	332	22·2±11 (4·0, 92·0)	188	23·5±11·8 (2·0, 74·0)	0·23
Pulse, beats per minute	332	81·5±12·9 (49·0, 114·0)	187	82·4±13·4 (50·0, 131·0)	0·44
Systolic blood pressure, mmHg	332	125·6±13·8 (91·0, 167·0)	187	124·9±15·6 (88·0, 186·0)	0·60
Diastolic blood pressure, mmHg	332	79·5±9·9 (57·0, 111·0)	187	78·6±9·9 (59·0, 116·0)	0·33

Abbreviations: SD, standard deviation; Min., minimum; Max., maximum; cm, centimeter; kg, kilogram; GED, general education diploma; CPD, cigarettes per day; PSCDI, Penn State Cigarette Dependence Index; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; CES-D, Center for Epidemiologic Studies Depression Scale; COPD, Chronic Obstructive Pulmonary Disease; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; BMI, body mass index; FEV1, Forced expiratory volume in one second; FVC, forced vital capacity; CO, carbon monoxide; CI, confidence interval.

^All baseline physiological measures obtained at week 0.

* Based on Wilcoxon-Mann-Whitney test.

Table S4. Retention outcome pre/post randomisation including reasons for withdrawal by condition and study period

Note: W=week. W0-W24 = study intervention period. W25-W36=follow-up period.

	Baseline	CIG SUB (N=130)		0 mg/ml (N=130)		8 mg/ml (N=130)		36 mg/ml (N=130)		Total
		W0-W24	W25-W36	W0-W24	W25-W36	W0-W24	W25-W36	W0-W24	W25-W36	
Retention pre-randomisation										
Failed at Visit 1 (inclusion-exclusion criteria)	90	..	..	..	..	..	..	..	..	90
Failed at Visit 2 (no show/inclusion-exclusion criteria)	73	..	..	..	..	..	..	..	..	73
Failed at Visit 2 for SAE (Death)	1	..	..	..	..	..	..	..	..	1
Subtotal	164	..	..	..	..	..	..	..	..	164
Retention post-randomisation										
Withdrawn	..	39	6	56	8	49	10	44	11	223
Participant decision	..	10	1	15	1	11	1	10	0	49
No reasons given	..	2	0	3	0	1	0	1	0	7
Unable to keep appointments	..	0	0	6	1	5	0	3	0	15
Did not like study product	..	0	0	2	0	3	0	1	0	6
Study location access	..	2	0	1	0	0	0	0	0	3
Personal reasons	..	6	1	1	0	2	1	4	0	15
Other*	..	0	0	2	0	0	0	1	0	3
PI decision	..	29	5	41	7	38	9	34	11	174
No show at three consecutive appointments	..	27	0	37	4	32	7	28	6	141
Missed final study visit (Visit 12)		..	5	..	2	..	2	..	4	13
Unable to use study product 2+ weeks	..	0	..	1	..	0	..	2	..	3
New pregnancy	..	0	0	0	0	1	0	1	1	3
Psychiatric hospitalization	..	1	0	2	1	0	0	0	0	4
Death	..	0	0	1	0	0	0	0	0	1
Other SAE^	..	1	0	0	0	2	0	1	0	4
Other[#]	..	0	0	0	0	3	0	2	0	5
Completed	..	91	85	74	66	81	71	86	75	297[1]
Subtotal	520									
Total (among participants who attended Visit 1)	684									

* Participant decision other (cessation medication use/trying to quit, N=1; participant reported the study was not benefiting them, N=1; participant reported negative physical/mental effects associated with study, N=1).

^ SAE (critical lab value at visit 2, N=1; new chronic disease diagnosis/hospitalization, N=3).

PI decision other (increased blood pressure, N=1; seizure during visit 2, N=1; AE that led to study product use discontinuation, N=1; medical history/visit 2 lab values, N=2).

Ł Participants completed full trial including both study intervention period and follow-up period.

Table S5. Summary of significance

Analysis	Control*	Pairwise comparison	Table number
Urinary total NNAL			
Between conditions at each time point using multiple imputation method unadjusted	W24	CS vs. 36 mg/ml	S11
Between conditions at each time point using last-observation-carried-forward method unadjusted	W24	0 mg/ml vs. 36 mg/ml	S15
Between conditions at each time point using multiple imputation method adjusted	W24	CS vs. 36 mg/ml	S11
Between conditions at each time point using intent-to-treat method adjusted	W24	CS vs. 36 mg/ml	S12
Between conditions at each time point using per-protocol method adjusted	W24	CS vs. 36 mg/ml	S13
Between conditions at each time point using baseline-carried-forward method adjusted	W24	CS vs. 36 mg/ml	S14
	W24	0 mg/ml vs. 36 mg/ml	S14
Between conditions at each time point using last-observation-carried-forward method adjusted	W12	0 mg/ml vs. 36 mg/ml	S15
	W24	0 mg/ml vs. 36 mg/ml	S15
Relative to baseline within each condition using multiple imputation method unadjusted	36 mg/ml	W12 vs. W0	S16
	36 mg/ml	W24 vs. W0	S16
Relative to baseline within each condition using intent-to-treat method unadjusted	36 mg/ml	W12 vs. W0	S17
	36 mg/ml	W24 vs. W0	S17
Relative to baseline within each condition using per-protocol method unadjusted	36 mg/ml	W12 vs. W0	S18
	36 mg/ml	W24 vs. W0	S18
Relative to baseline within each condition using baseline-carried-forward method unadjusted	36 mg/ml	W12 vs. W0	S19
	36 mg/ml	W24 vs. W0	S19
Relative to baseline within each condition using last-observation-carried-forward method unadjusted	36 mg/ml	W4 vs. W0	S20
	36 mg/ml	W12 vs. W0	S20
	36 mg/ml	W24 vs. W0	S20
Relative to baseline within each condition using multiple imputation method adjusted	36 mg/ml	W12 vs. W0	S16
	36 mg/ml	W24 vs. W0	S16
Relative to baseline within each condition using intent-to-treat method adjusted	36 mg/ml	W12 vs. W0	S17
	36 mg/ml	W24 vs. W0	S17
Relative to baseline within each condition using per-protocol method adjusted	36 mg/ml	W12 vs. W0	S18
	36 mg/ml	W24 vs. W0	S18
Relative to baseline within each condition using baseline-carried-forward method adjusted	36 mg/ml	W12 vs. W0	S19
	36 mg/ml	W24 vs. W0	S19
Relative to baseline within each condition using last-observation-carried-forward method adjusted	36 mg/ml	W4 vs. W0	S20
	36 mg/ml	W12 vs. W0	S20

	36 mg/ml	W24 vs. W0	S20
Urinary cotinine			
Between conditions at each time point using intent-to-treat method adjusted	W4	8 mg/ml vs. 36 mg/ml	S27
Between conditions at each time point using baseline-carried-forward method adjusted	W4	8 mg/ml vs. 36 mg/ml	S29
Relative to baseline within each condition using multiple imputation method unadjusted	8 mg/ml	W4 vs. W0	S31
	8 mg/ml	W12 vs. W0	S31
	8 mg/ml	W24 vs. W0	S31
Relative to baseline within each condition using intent-to-treat method unadjusted	8 mg/ml	W4 vs. W0	S32
	8 mg/ml	W12 vs. W0	S32
	8 mg/ml	W24 vs. W0	S32
Relative to baseline within each condition using per-protocol method unadjusted	8 mg/ml	W12 vs. W0	S33
Relative to baseline within each condition using baseline-carried-forward method unadjusted	8 mg/ml	W4 vs. W0	S34
	8 mg/ml	W12 vs. W0	S34
Relative to baseline within each condition using last-observation-carried-forward method unadjusted	8 mg/ml	W4 vs. W0	S35
	8 mg/ml	W12 vs. W0	S35
	8 mg/ml	W24 vs. W0	S35
Relative to baseline within each condition using multiple imputation method adjusted	CS	W12 vs. W0	S31
	8 mg/ml	W4 vs. W0	S31
	8 mg/ml	W12 vs. W0	S31
	8 mg/ml	W24 vs. W0	S31
Relative to baseline within each condition using intent-to-treat method adjusted	8 mg/ml	W4 vs. W0	S32
	8 mg/ml	W12 vs. W0	S32
	8 mg/ml	W24 vs. W0	S32
Relative to baseline within each condition using per-protocol method adjusted	8 mg/ml	W24 vs. W0	S33
Relative to baseline within each condition using baseline-carried-forward method adjusted	8 mg/ml	W4 vs. W0	S34
	8 mg/ml	W12 vs. W0	S34
Relative to baseline within each condition using last-observation-carried-forward method adjusted	8 mg/ml	W4 vs. W0	S35
	8 mg/ml	W12 vs. W0	S35
	8 mg/ml	W24 vs. W0	S35
Exhaled carbon monoxide			
Between conditions at each time point using multiple imputation method unadjusted	W1	CS vs. 8 mg/ml	S41
	W1	CS vs. 36 mg/ml	S41
	W1	0 mg/ml vs. 8 mg/ml	S41
	W2	CS vs. 8 mg/ml	S41

	W2	0 mg/ml vs. 8 mg/ml	S41
	W4	CS vs. 8 mg/ml	S41
	W4	CS vs. 36 mg/ml	S41
	W4	0 mg/ml vs. 8 mg/ml	S41
	W4	0 mg/ml vs. 36 mg/ml	S41
	W8	CS vs. 8 mg/ml	S41
	W8	CS vs. 36 mg/ml	S41
	W12	0 mg/ml vs. 8 mg/ml	S41
	W12	0 mg/ml vs. 36 mg/ml	S41
	W16	CS vs. 8 mg/ml	S41
	W16	CS vs. 36 mg/ml	S41
	W16	0 mg/ml vs. 8 mg/ml	S41
	W16	0 mg/ml vs. 36 mg/ml	S41
	W20	CS vs. 8 mg/ml	S41
	W20	CS vs. 36 mg/ml	S41
	W20	0 mg/ml vs. 8 mg/ml	S41
	W20	0 mg/ml vs. 36 mg/ml	S41
	W24	CS vs. 36 mg/ml	S41
	W24	0 mg/ml vs. 36 mg/ml	S41
Between conditions at each time point using intent-to-treat method unadjusted	W1	CS vs. 8 mg/ml	S42
	W1	0 mg/ml vs. 8 mg/ml	S42
	W2	CS vs. 8 mg/ml	S42
	W2	CS vs. 36 mg/ml	S42
	W2	0 mg/ml vs. 8 mg/ml	S42
	W4	CS vs. 8 mg/ml	S42
	W4	CS vs. 36 mg/ml	S42
	W4	0 mg/ml vs. 36 mg/ml	S42
	W8	CS vs. 8 mg/ml	S42
	W8	CS vs. 36 mg/ml	S42
	W12	0 mg/ml vs. 36 mg/ml	S42
	W16	CS vs. 8 mg/ml	S42
	W16	CS vs. 36 mg/ml	S42
	W16	0 mg/ml vs. 8 mg/ml	S42
	W16	0 mg/ml vs. 36 mg/ml	S42
	W20	CS vs. 8 mg/ml	S42
	W20	CS vs. 36 mg/ml	S42

	W20	0 mg/ml vs. 36 mg/ml	S42
Between conditions at each time point using per-protocol method unadjusted	W1	CS vs. 8 mg/ml	S43
	W2	CS vs. 8 mg/ml	S43
	W4	CS vs. 8 mg/ml	S43
	W4	CS vs. 36 mg/ml	S43
	W8	CS vs. 8 mg/ml	S43
	W8	CS vs. 36 mg/ml	S43
	W12	0 mg/ml vs. 36 mg/ml	S43
	W16	CS vs. 8 mg/ml	S43
	W16	CS vs. 36 mg/ml	S43
	W16	0 mg/ml vs. 8 mg/ml	S43
	W16	0 mg/ml vs. 36 mg/ml	S43
	W20	CS vs. 8 mg/ml	S43
	W20	CS vs. 36 mg/ml	S43
	W20	0 mg/ml vs. 36 mg/ml	S43
	W24	CS vs. 36 mg/ml	S43
Between conditions at each time point using baseline-carried-forward method unadjusted	W1	CS vs. 8 mg/ml	S44
	W1	0 mg/ml vs. 8 mg/ml	S44
	W2	CS vs. 8 mg/ml	S44
	W2	CS vs. 36 mg/ml	S44
	W2	0 mg/ml vs. 8 mg/ml	S44
	W4	CS vs. 8 mg/ml	S44
	W4	CS vs. 36 mg/ml	S44
	W4	0 mg/ml vs. 8 mg/ml	S44
	W4	0 mg/ml vs. 36 mg/ml	S44
	W8	CS vs. 8 mg/ml	S44
	W8	CS vs. 36 mg/ml	S44
	W8	0 mg/ml vs. 36 mg/ml	S44
	W12	0 mg/ml vs. 8 mg/ml	S44
	W12	0 mg/ml vs. 36 mg/ml	S44
	W16	CS vs. 8 mg/ml	S44
	W16	CS vs. 36 mg/ml	S44
	W16	0 mg/ml vs. 8 mg/ml	S44
	W16	0 mg/ml vs. 36 mg/ml	S44
	W20	CS vs. 8 mg/ml	S44
	W20	CS vs. 36 mg/ml	S44

	W20	0 mg/ml vs. 8 mg/ml	S44
	W20	0 mg/ml vs. 36 mg/ml	S44
	W24	0 mg/ml vs. 36 mg/ml	S44
Between conditions at each time point using last-observation-carried-forward method unadjusted	W1	CS vs. 8 mg/ml	S45
	W1	0 mg/ml vs. 8 mg/ml	S45
	W2	CS vs. 8 mg/ml	S45
	W2	CS vs. 36 mg/ml	S45
	W2	0 mg/ml vs. 8 mg/ml	S45
	W4	CS vs. 8 mg/ml	S45
	W4	CS vs. 36 mg/ml	S45
	W4	0 mg/ml vs. 8 mg/ml	S45
	W4	0 mg/ml vs. 36 mg/ml	S45
	W8	CS vs. 8 mg/ml	S45
	W8	CS vs. 36 mg/ml	S45
	W8	0 mg/ml vs. 8 mg/ml	S45
	W8	0 mg/ml vs. 36 mg/ml	S45
	W12	0 mg/ml vs. 8 mg/ml	S45
	W12	0 mg/ml vs. 36 mg/ml	S45
	W16	CS vs. 8 mg/ml	S45
	W16	CS vs. 36 mg/ml	S45
	W16	0 mg/ml vs. 8 mg/ml	S45
	W16	0 mg/ml vs. 36 mg/ml	S45
	W20	CS vs. 8 mg/ml	S45
	W20	CS vs. 36 mg/ml	S45
	W20	0 mg/ml vs. 8 mg/ml	S45
	W20	0 mg/ml vs. 36 mg/ml	S45
	W24	0 mg/ml vs. 8 mg/ml	S45
	W24	0 mg/ml vs. 36 mg/ml	S45
Between conditions at each time point using multiple imputation method adjusted	W1	CS vs. 8 mg/ml	S41
	W1	0 mg/ml vs. 8 mg/ml	S41
	W2	CS vs. 8 mg/ml	S41
	W4	CS vs. 8 mg/ml	S41
	W4	CS vs. 36 mg/ml	S41
	W4	0 mg/ml vs. 8 mg/ml	S41
	W4	0 mg/ml vs. 36 mg/ml	S41
	W8	CS vs. 8 mg/ml	S41

	W8	CS vs. 36 mg/ml	S41
	W12	0 mg/ml vs. 36 mg/ml	S41
	W16	CS vs. 8 mg/ml	S41
	W16	CS vs. 36 mg/ml	S41
	W16	0 mg/ml vs. 8 mg/ml	S41
	W16	0 mg/ml vs. 36 mg/ml	S41
	W20	CS vs. 36 mg/ml	S41
	W20	0 mg/ml vs. 8 mg/ml	S41
	W20	0 mg/ml vs. 36 mg/ml	S41
	W24	CS vs. 36 mg/ml	S41
Between conditions at each time point using intent-to-treat method adjusted	W1	CS vs. 8 mg/ml	S42
	W2	CS vs. 8 mg/ml	S42
	W2	CS vs. 36 mg/ml	S42
	W4	CS vs. 8 mg/ml	S42
	W4	CS vs. 36 mg/ml	S42
	W8	CS vs. 8 mg/ml	S42
	W8	CS vs. 36 mg/ml	S42
	W12	0 mg/ml vs. 8 mg/ml	S42
	W12	0 mg/ml vs. 36 mg/ml	S42
	W16	CS vs. 8 mg/ml	S42
	W16	CS vs. 36 mg/ml	S42
	W16	0 mg/ml vs. 8 mg/ml	S42
	W16	0 mg/ml vs. 36 mg/ml	S42
	W20	CS vs. 36 mg/ml	S42
	W20	0 mg/ml vs. 36 mg/ml	S42
	W24	CS vs. 36 mg/ml	S42
Between conditions at each time point using per-protocol method adjusted	W1	CS vs. 8 mg/ml	S43
	W2	CS vs. 8 mg/ml	S43
	W4	CS vs. 8 mg/ml	S43
	W4	CS vs. 36 mg/ml	S43
	W8	CS vs. 36 mg/ml	S43
	W12	0 mg/ml vs. 36 mg/ml	S43
	W16	CS vs. 8 mg/ml	S43
	W16	CS vs. 36 mg/ml	S43
	W16	0 mg/ml vs. 8 mg/ml	S43
	W16	0 mg/ml vs. 36 mg/ml	S43

	W20	CS vs. 36 mg/ml	S43
	W20	0 mg/ml vs. 36 mg/ml	S43
	W24	CS vs. 36 mg/ml	S43
Between conditions at each time point using baseline-carried-forward method adjusted	W1	CS vs. 8 mg/ml	S44
	W2	CS vs. 8 mg/ml	S44
	W2	CS vs. 36 mg/ml	S44
	W4	CS vs. 8 mg/ml	S44
	W4	CS vs. 36 mg/ml	S44
	W4	0 mg/ml vs. 8 mg/ml	S44
	W4	0 mg/ml vs. 36 mg/ml	S44
	W8	CS vs. 36 mg/ml	S44
	W12	0 mg/ml vs. 8 mg/ml	S44
	W12	0 mg/ml vs. 36 mg/ml	S44
	W16	CS vs. 8 mg/ml	S44
	W16	CS vs. 36 mg/ml	S44
	W16	0 mg/ml vs. 8 mg/ml	S44
	W16	0 mg/ml vs. 36 mg/ml	S44
	W20	CS vs. 36 mg/ml	S44
	W20	0 mg/ml vs. 8 mg/ml	S44
	W20	0 mg/ml vs. 36 mg/ml	S44
	W24	0 mg/ml vs. 36 mg/ml	S44
Between conditions at each time point using last-observation-carried-forward method adjusted	W1	CS vs. 8 mg/ml	S45
	W2	CS vs. 8 mg/ml	S45
	W2	CS vs. 36 mg/ml	S45
	W4	CS vs. 8 mg/ml	S45
	W4	CS vs. 36 mg/ml	S45
	W8	CS vs. 8 mg/ml	S45
	W8	CS vs. 36 mg/ml	S45
	W12	0 mg/ml vs. 8 mg/ml	S45
	W12	0 mg/ml vs. 36 mg/ml	S45
	W16	CS vs. 8 mg/ml	S45
	W16	CS vs. 36 mg/ml	S45
	W16	0 mg/ml vs. 8 mg/ml	S45
	W16	0 mg/ml vs. 36 mg/ml	S45
	W20	CS vs. 8 mg/ml	S45
	W20	CS vs. 36 mg/ml	S45

	W20	0 mg/ml vs. 8 mg/ml	S45
	W20	0 mg/ml vs. 36 mg/ml	S45
Relative to baseline within each condition using multiple imputation method unadjusted	0 mg/ml	W2 vs. W0	S46
	8 mg/ml	All weeks except week 24	S46
	36 mg/ml	All weeks	S46
Relative to baseline within each condition using intent-to-treat method unadjusted	CS	W1 vs. W0	S47
	CS	W4 vs. W0	S47
	CS	W12 vs. W0	S47
	0 mg/ml	W1 vs. W0	S47
	0 mg/ml	W2 vs. W0	S47
	0 mg/ml	W4 vs. W0	S47
	0 mg/ml	W8 vs. W0	S47
	8 mg/ml	All weeks	S47
	36 mg/ml	All weeks	S47
Relative to baseline within each condition using per-protocol method unadjusted	8 mg/ml	All weeks except week 24	S48
	36 mg/ml	All weeks	S48
Relative to baseline within each condition using baseline-carried-forward method unadjusted	CS	W1 vs. W0	S49
	0 mg/ml	W1 vs. W0	S49
	8 mg/ml	All weeks except week 20, week 24	S49
	36 mg/ml	All weeks except week 16	S49
Relative to baseline within each condition using last-observation-carried-forward method unadjusted	CS	W1 vs. W0	S50
	CS	W4 vs. W0	S50
	CS	W12 vs. W0	S50
	0 mg/ml	W1 vs. W0	S50
	0 mg/ml	W2 vs. W0	S50
	0 mg/ml	W4 vs. W0	S50
	8 mg/ml	All weeks	S50
	36 mg/ml	All weeks	S50
Relative to baseline within each condition using multiple imputation method adjusted	CS	W4 vs. W0	S46
	CS	W12 vs. W0	S46
	0 mg/ml	W2 vs. W0	S46
	0 mg/ml	W4 vs. W0	S46
	8 mg/ml	All weeks	S46
	36 mg/ml	All weeks	S46

Relative to baseline within each condition using intent-to-treat method adjusted	CS	W1 vs. W0	S47
	CS	W4 vs. W0	S47
	CS	W12 vs. W0	S47
	0 mg/ml	W1 vs. W0	S47
	0 mg/ml	W2 vs. W0	S47
	0 mg/ml	W4 vs. W0	S47
	0 mg/ml	W8 vs. W0	S47
	8 mg/ml	All weeks	S47
	36 mg/ml	All weeks	S47
Relative to baseline within each condition using per-protocol method adjusted	8 mg/ml	All weeks except week 24	S48
	36 mg/ml	All weeks	S48
Relative to baseline within each condition using baseline-carried-forward method adjusted	CS	W1 vs. W0	S49
	0 mg/ml	W1 vs. W0	S49
	0 mg/ml	W2 vs. W0	S49
	8 mg/ml	All weeks except week 24	S49
	36 mg/ml	All weeks	S49
Relative to baseline within each condition using last-observation-carried-forward method adjusted	CS	W1 vs. W0	S50
	CS	W4 vs. W0	S50
	CS	W12 vs. W0	S50
	CS	W24 vs. W0	S50
	0 mg/ml	W1 vs. W0	S50
	0 mg/ml	W2 vs. W0	S50
	0 mg/ml	W4 vs. W0	S50
	0 mg/ml	W8 vs. W0	S50
	8 mg/ml	All weeks	S50
	36 mg/ml	All weeks	S50
Cigarettes smoked per day			
Between conditions at each time point using multiple imputation method unadjusted	W1	CS vs. 36 mg/ml	S56
	W2	CS vs. 36 mg/ml	S56
	W4	CS vs. 0 mg/ml	S56
	W4	CS vs. 8 mg/ml	S56
	W4	CS vs. 36 mg/ml	S56
	W8	CS vs. 0 mg/ml	S56
	W8	CS vs. 36 mg/ml	S56
	W12	CS vs. 36 mg/ml	S56

	W16	CS vs. 0 mg/ml	S56
	W16	CS vs. 36 mg/ml	S56
	W20	CS vs. 36 mg/ml	S56
	W24	CS vs. 36 mg/ml	S56
Between conditions at each time point using intent-to-treat method unadjusted	W1	CS vs. 36 mg/ml	S57
	W2	CS vs. 8 mg/ml	S57
	W2	CS vs. 36 mg/ml	S57
	W4	CS vs. 0 mg/ml	S57
	W4	CS vs. 8 mg/ml	S57
	W4	CS vs. 36 mg/ml	S57
	W8	CS vs. 0 mg/ml	S57
	W8	CS vs. 8 mg/ml	S57
	W8	CS vs. 36 mg/ml	S57
	W12	CS vs. 8 mg/ml	S57
	W12	CS vs. 36 mg/ml	S57
	W16	CS vs. 0 mg/ml	S57
	W16	CS vs. 36 mg/ml	S57
	W20	CS vs. 8 mg/ml	S57
	W20	CS vs. 36 mg/ml	S57
	W24	CS vs. 8 mg/ml	S57
	W24	CS vs. 36 mg/ml	S57
Between conditions at each time point using per-protocol method unadjusted	W1	CS vs. 36 mg/ml	S58
	W2	CS vs. 0 mg/ml	S58
	W2	CS vs. 8 mg/ml	S58
	W2	CS vs. 36 mg/ml	S58
	W4	CS vs. 0 mg/ml	S58
	W4	CS vs. 8 mg/ml	S58
	W4	CS vs. 36 mg/ml	S58
	W8	CS vs. 0 mg/ml	S58
	W8	CS vs. 8 mg/ml	S58
	W8	CS vs. 36 mg/ml	S58
	W12	CS vs. 8 mg/ml	S58
	W12	CS vs. 36 mg/ml	S58
	W16	CS vs. 0 mg/ml	S58
	W16	CS vs. 36 mg/ml	S58
	W20	CS vs. 8 mg/ml	S58

	W20	CS vs. 36 mg/ml	S58
	W24	CS vs. 0 mg/ml	S58
	W24	CS vs. 8 mg/ml	S58
	W24	CS vs. 36 mg/ml	S58
Between conditions at each time point using baseline-carried-forward method unadjusted	W1	CS vs. 36 mg/ml	S59
	W2	CS vs. 36 mg/ml	S59
	W4	CS vs. 36 mg/ml	S59
	W8	CS vs. 36 mg/ml	S59
	W12	CS vs. 36 mg/ml	S59
	W16	CS vs. 36 mg/ml	S59
	W20	0 mg/ml vs. 36 mg/ml	S59
Between conditions at each time point using last-observation-carried-forward method unadjusted	W1	CS vs. 36 mg/ml	S60
	W2	CS vs. 36 mg/ml	S60
	W4	CS vs. 8 mg/ml	S60
	W4	CS vs. 36 mg/ml	S60
	W8	CS vs. 8 mg/ml	S60
	W8	CS vs. 36 mg/ml	S60
	W12	CS vs. 36 mg/ml	S60
	W16	CS vs. 36 mg/ml	S60
	W20	CS vs. 36 mg/ml	S60
	W20	0 mg/ml vs. 36 mg/ml	S60
	W24	CS vs. 36 mg/ml	S60
	W24	0 mg/ml vs. 36 mg/ml	S60
Between conditions at each time point using multiple imputation method adjusted	W1	CS vs. 0 mg/ml	S56
	W1	CS vs. 8 mg/ml	S56
	W1	CS vs. 36 mg/ml	S56
	W2	CS vs. 0 mg/ml	S56
	W2	CS vs. 8 mg/ml	S56
	W2	CS vs. 36 mg/ml	S56
	W4	CS vs. 0 mg/ml	S56
	W4	CS vs. 8 mg/ml	S56
	W4	CS vs. 36 mg/ml	S56
	W8	CS vs. 0 mg/ml	S56
	W8	CS vs. 8 mg/ml	S56
	W8	CS vs. 36 mg/ml	S56
	W12	CS vs. 0 mg/ml	S56

	W12	CS vs. 36 mg/ml	S56
	W16	CS vs. 0 mg/ml	S56
	W16	CS vs. 8 mg/ml	S56
	W16	CS vs. 36 mg/ml	S56
	W20	CS vs. 0 mg/ml	S56
	W20	CS vs. 8 mg/ml	S56
	W20	CS vs. 36 mg/ml	S56
	W24	CS vs. 0 mg/ml	S56
	W24	CS vs. 8 mg/ml	S56
	W24	CS vs. 36 mg/ml	S56
Between conditions at each time point using intent-to-treat method adjusted	W1	CS vs. 0 mg/ml	S57
	W1	CS vs. 8 mg/ml	S57
	W1	CS vs. 36 mg/ml	S57
	W2	CS vs. 0 mg/ml	S57
	W2	CS vs. 8 mg/ml	S57
	W2	CS vs. 36 mg/ml	S57
	W4	CS vs. 0 mg/ml	S57
	W4	CS vs. 8 mg/ml	S57
	W4	CS vs. 36 mg/ml	S57
	W8	CS vs. 0 mg/ml	S57
	W8	CS vs. 8 mg/ml	S57
	W8	CS vs. 36 mg/ml	S57
	W12	CS vs. 0 mg/ml	S57
	W12	CS vs. 8 mg/ml	S57
	W12	CS vs. 36 mg/ml	S57
	W16	CS vs. 0 mg/ml	S57
	W16	CS vs. 8 mg/ml	S57
	W16	CS vs. 36 mg/ml	S57
	W20	CS vs. 0 mg/ml	S57
	W20	CS vs. 8 mg/ml	S57
	W20	CS vs. 36 mg/ml	S57
	W24	CS vs. 0 mg/ml	S57
	W24	CS vs. 8 mg/ml	S57
	W24	CS vs. 36 mg/ml	S57
Between conditions at each time point using per-protocol method adjusted	W1	CS vs. 0 mg/ml	S58
	W1	CS vs. 8 mg/ml	S58

	W1	CS vs. 36 mg/ml	S58
	W2	CS vs. 0 mg/ml	S58
	W2	CS vs. 8 mg/ml	S58
	W2	CS vs. 36 mg/ml	S58
	W4	CS vs. 0 mg/ml	S58
	W4	CS vs. 8 mg/ml	S58
	W4	CS vs. 36 mg/ml	S58
	W8	CS vs. 0 mg/ml	S58
	W8	CS vs. 8 mg/ml	S58
	W8	CS vs. 36 mg/ml	S58
	W12	CS vs. 0 mg/ml	S58
	W12	CS vs. 8 mg/ml	S58
	W12	CS vs. 36 mg/ml	S58
	W16	CS vs. 0 mg/ml	S58
	W16	CS vs. 36 mg/ml	S58
	W20	CS vs. 0 mg/ml	S58
	W20	CS vs. 8 mg/ml	S58
	W20	CS vs. 36 mg/ml	S58
	W24	CS vs. 0 mg/ml	S58
	W24	CS vs. 8 mg/ml	S58
	W24	CS vs. 36 mg/ml	S58
Between conditions at each time point using baseline-carried-forward method adjusted	W1	CS vs. 8 mg/ml	S59
	W1	CS vs. 36 mg/ml	S59
	W2	CS vs. 0 mg/ml	S59
	W2	CS vs. 8 mg/ml	S59
	W2	CS vs. 36 mg/ml	S59
	W4	CS vs. 0 mg/ml	S59
	W4	CS vs. 8 mg/ml	S59
	W4	CS vs. 36 mg/ml	S59
	W8	CS vs. 0 mg/ml	S59
	W8	CS vs. 8 mg/ml	S59
	W8	CS vs. 36 mg/ml	S59
	W12	CS vs. 36 mg/ml	S59
	W16	CS vs. 36 mg/ml	S59
Between conditions at each time point using last-observation-carried-forward method adjusted	W1	CS vs. 8 mg/ml	S60
	W1	CS vs. 36 mg/ml	S60

	W2	CS vs. 0 mg/ml	S60
	W2	CS vs. 8 mg/ml	S60
	W2	CS vs. 36 mg/ml	S60
	W4	CS vs. 0 mg/ml	S60
	W4	CS vs. 8 mg/ml	S60
	W4	CS vs. 36 mg/ml	S60
	W8	CS vs. 0 mg/ml	S60
	W8	CS vs. 8 mg/ml	S60
	W8	CS vs. 36 mg/ml	S60
	W12	CS vs. 8 mg/ml	S60
	W12	CS vs. 36 mg/ml	S60
	W16	CS vs. 0 mg/ml	S60
	W16	CS vs. 8 mg/ml	S60
	W16	CS vs. 36 mg/ml	S60
	W20	CS vs. 8 mg/ml	S60
	W20	CS vs. 36 mg/ml	S60
	W20	0 mg/ml vs. 36 mg/ml	S60
	W24	CS vs. 8 mg/ml	S60
	W24	CS vs. 36 mg/ml	S60
Relative to baseline within each condition using multiple imputation method unadjusted	CS	All weeks	S61
	0 mg/ml	All weeks	S61
	8 mg/ml	All weeks	S61
	36 mg/ml	All weeks	S61
Relative to baseline within each condition using intent-to-treat method unadjusted	CS	All weeks	S62
	0 mg/ml	All weeks	S62
	8 mg/ml	All weeks	S62
	36 mg/ml	All weeks	S62
Relative to baseline within each condition using per-protocol method unadjusted	CS	All weeks	S63
	0 mg/ml	All weeks	S63
	8 mg/ml	All weeks	S63
	36 mg/ml	All weeks	S63
Relative to baseline within each condition using baseline-carried-forward method unadjusted	CS	All weeks	S64
	0 mg/ml	All weeks	S64
	8 mg/ml	All weeks	S64
	36 mg/ml	All weeks	S64

Relative to baseline within each condition using last-observation-carried-forward method unadjusted	CS	All weeks	S65
	0 mg/ml	All weeks	S65
	8 mg/ml	All weeks	S65
	36 mg/ml	All weeks	S65
Relative to baseline within each condition using multiple imputation method adjusted	CS	All weeks	S61
	0 mg/ml	All weeks	S61
	8 mg/ml	All weeks	S61
	36 mg/ml	All weeks	S61
Relative to baseline within each condition using intent-to-treat method adjusted	CS	All weeks	S62
	0 mg/ml	All weeks	S62
	8 mg/ml	All weeks	S62
	36 mg/ml	All weeks	S62
Relative to baseline within each condition using per-protocol method adjusted	CS	All weeks	S63
	0 mg/ml	All weeks	S63
	8 mg/ml	All weeks	S63
	36 mg/ml	All weeks	S63
Relative to baseline within each condition using baseline-carried-forward method adjusted	CS	All weeks	S64
	0 mg/ml	All weeks	S64
	8 mg/ml	All weeks	S64
	36 mg/ml	All weeks	S64
Relative to baseline within each condition using last-observation-carried-forward method adjusted	CS	All weeks	S65
	0 mg/ml	All weeks	S65
	8 mg/ml	All weeks	S65
	36 mg/ml	All weeks	S65
Study product use			
Between conditions at each time point using intent-to-treat method with assumption of no use to missing	W16	CS vs. 36 mg/ml	S69
	W4	0 mg/ml vs. 36 mg/ml	S69
Between conditions at each time point using intent-to-treat method without assumption of no use to missing	W8	CS vs. 0 mg/ml	S70
	W16	CS vs. 0 mg/ml	S70
	W8	CS vs. 8 mg/ml	S70
	W12	CS vs. 8 mg/ml	S70
	W16	CS vs. 8 mg/ml	S70
	All weeks except W1	CS vs. 36 mg/ml	S70
Between conditions at each time point using per-protocol method	W4	CS vs. 0 mg/ml	S71

	W8	CS vs. 0 mg/ml	S71
	W16	CS vs. 0 mg/ml	S71
	W8	CS vs. 8 mg/ml	S71
	W12	CS vs. 8 mg/ml	S71
	W16	CS vs. 8 mg/ml	S71
	All weeks except W1	CS vs. 36 mg/ml	S71
Relative to week 1 within each condition using intent-to-treat method with assumption of no use to missing	CS	All weeks except W2	S72
	0 mg/ml	All weeks except W2	S72
	8 mg/ml	All weeks except W2, W4	S72
	36 mg/ml	All weeks except W2, W4	S72
Relative to week 1 within each condition using intent-to-treat method with assumption of no use to missing	CS	All weeks except W2	S73
	0 mg/ml	All weeks except W2	S73
	8 mg/ml	All weeks except W2	S73
	36 mg/ml	All weeks except W2, W4	S73
Relative to week 1 within each condition using per-protocol method	CS	All weeks except W2	S74
	0 mg/ml	All weeks except W2, W4, W8	S74
	8 mg/ml	All weeks except W2, W4	S74
	36 mg/ml	W12 vs. W1	S74
	36 mg/ml	W20 vs. W1	S74
	36 mg/ml	W24 vs. W1	S74

Abbreviation: W, week; CS, cigarette substitute.

*Analysis is controlled for the condition or the visit.

Table S6. Estimated urinary total NNAL standardized by creatinine in unadjusted and adjusted mixed models using multiple imputation method

NNAL, pg/mg creatinine*	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	**N**	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)
Week 0	130	377·38 (296·91, 482·5)	130	416·47 (326·89, 533·79)	130	397·24 (312·15, 508·54)	130	389·13 (305·93, 497·90)
Week 4	130	352·14 (276·18, 451·71)	130	399·70 (308·01, 522·31)	130	336·05 (264·03, 430·26)	130	293·71 (230·91, 375·79)
Week 12	130	316·46 (245·66, 410·38)	130	347·22 (255·55, 476·37)	130	342·09 (265·39, 443·88)	130	238·96 (188·35, 304·93)
Week 24	130	346·09 (265·00, 455·32)	130	332·43 (254·31, 437·78)	130	271·21 (196·99, 377·36)	130	210·80 (163·03, 274·42)
	Adjusted Model							
Week 0	130	357·01 (291·52, 439·05)	130	358·52 (291·68, 442·59)	130	356·84 (290·63, 440·03)	130	356·43 (290·37, 439·41)
Week 4	130	333·25 (269·99, 413·21)	130	344·29 (277·47, 429·24)	130	302·41 (246·36, 372·81)	130	269·68 (218·36, 334·59)
Week 12	130	299·67 (241·39, 373·79)	130	299·71 (232·67, 388·62)	130	307·79 (246·35, 386·51)	130	219·79 (180·51, 268·69)
Week 24	130	327·56 (256·19, 421·41)	130	287·13 (226·09, 366·79)	130	244·60 (181·88, 331·94)	130	194·09 (152·36, 248·74)

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation.

Table S7. Estimated urinary total NNAL standardized by creatinine in unadjusted and adjusted mixed models using intent-to-treat method

NNAL, pg/mg creatinine*	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**
Week 0	130	377·38 (297·40, 481·66)	130	416·47 (327·44, 532·85)	130	397·24 (312·67, 507·65)	130	389·13 (306·44, 497·03)
Week 4	115	350·75 (274·02, 451·79)	96	424·22 (324·17, 559·30)	110	319·86 (249·44, 412·76)	111	295·09 (230·81, 379·61)
Week 12	92	326·01 (249·32, 429·45)	77	368·19 (274·06, 499·11)	85	346·58 (262·34, 461·55)	93	253·31 (194·96, 331·46)
Week 24	90	342·76 (259·53, 456·31)	69	344·97 (252·03, 477·01)	73	255·78 (190·65, 346·22)	79	233·04 (175·83, 311·4)
	Adjusted Model							
Week 0	130	358·22 (292·32, 440·83)	130	360·37 (293·06, 445·09)	130	356·00 (289·39, 439·87)	130	358·74 (292·23, 442·28)
Week 4	115	329·87 (267·28, 408·96)	96	370·36 (293·95, 469·20)	110	299·70 (241·6, 373·54)	111	272·03 (219·97, 337·97)
Week 12	92	304·14 (242·18, 383·98)	77	319·41 (248·29, 413·58)	85	325·44 (255·64, 416·78)	93	226·21 (180·64, 284·74)
Week 24	90	329·08 (260·68, 417·73)	69	309·62 (237·43, 406·70)	73	250·17 (194·46, 323·94)	79	196·37 (154·47, 251·11)

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation.

Table S8. Estimated urinary total NNAL standardized by creatinine in unadjusted and adjusted mixed models using per-protocol method

NNAL, pg/mg creatinine*	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**
Week 0	85	379·67 (284·88, 510·32)	67	361·69 (262·27, 504·15)	66	359·26 (259·94, 501·92)	77	471·70 (346·63, 648·22)
Week 4	85	348·06 (261·80, 466·61)	67	375·23 (271·77, 523·67)	66	275·11 (200·73, 380·93)	77	337·99 (250·85, 459·58)
Week 12	85	342·09 (257·44, 458·38)	67	316·66 (230·58, 439·41)	66	334·78 (242·77, 466·60)	77	253·84 (189·97, 342·13)
Week 24	85	359·89 (270·45, 482·96)	67	321·11 (233·72, 445·80)	66	251·06 (183·71, 346·59)	77	239·78 (179·74, 322·63)
	Adjusted Model							
Week 0	85	338·14 (260·59, 441·84)	67	319·58 (237·92, 433·14)	66	327·97 (244·80, 443·28)	77	361·87 (272·23, 485·05)
Week 4	85	310·29 (239·66, 404·51)	67	331·39 (246·45, 449·65)	66	259·06 (194·67, 347·65)	77	261·52 (198·52, 347·23)
Week 12	85	305·03 (235·70, 397·47)	67	280·25 (209·43, 378·30)	66	309·49 (231·39, 417·56)	77	197·82 (151·29, 260·58)
Week 24	85	320·72 (247·50, 418·48)	67	284·14 (212·25, 383·72)	66	231·38 (174·42, 309·48)	77	187·13 (143·32, 246·11)

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed). Sample size included participants who have available urinary total NNAL at week 0, 4, 12 and 24, which is N=85, 67, 66 and 77 for CS, 0 mg/ml, 8 mg/ml and 36 mg/ml, respectively.

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation.

Table S9. Estimated urinary total NNAL standardized by creatinine in unadjusted and adjusted mixed models using baseline-carried-forward method

NNAL, pg/mg creatinine*	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**
Week 0	130	377·38 (297·73, 481·10)	130	416·47 (327·80, 532·22)	130	397·24 (313·02, 507·06)	130	389·13 (306·78, 496·46)
Week 4	130	346·29 (273·75, 440·54)	130	427·53 (336·31, 546·73)	130	340·38 (269·18, 432·83)	130	306·32 (242·84, 388·54)
Week 12	130	331·46 (262·29, 421·22)	130	387·44 (305·48, 494·25)	130	371·52 (293·22, 473·45)	130	271·00 (215·44, 342·72)
Week 24	130	360·57 (284·77, 459·15)	130	392·68 (309·51, 501·10)	130	330·25 (261·35, 419·64)	130	254·30 (202·45, 321·12)
	Adjusted Model							
Week 0	130	367·94 (307·16, 442·21)	130	369·15 (307·39, 444·84)	130	365·96 (304·64, 441·14)	130	369·14 (307·64, 444·43)
Week 4	130	337·70 (282·35, 405·23)	130	378·84 (315·31, 456·74)	130	318·57 (265·85, 383·01)	130	290·95 (243·51, 348·75)
Week 12	130	323·27 (270·49, 387·60)	130	343·72 (286·58, 413·64)	130	344·40 (287·00, 414·67)	130	257·56 (216·02, 308·04)
Week 24	130	351·59 (293·75, 422·20)	130	348·31 (290·34, 419·27)	130	305·69 (255·30, 367·25)	130	241·76 (203·00, 288·83)

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation.

Table S10. Estimated urinary total NNAL standardized by creatinine in unadjusted and adjusted mixed models using last-observation-carried-forward method

NNAL, pg/mg creatinine*	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)
Week 0	130	377·38 (297·94, 480·75)	130	416·47 (328·03, 531·84)	130	397·24 (313·24, 506·69)	130	389·13 (306·99, 496·09)
Week 4	130	346·29 (273·94, 440·23)	130	427·53 (336·54, 546·32)	130	340·38 (269·37, 432·52)	130	306·32 (243·00, 388·26)
Week 12	130	326·88 (258·93, 414·97)	130	408·92 (322·23, 521·96)	130	369·69 (292·01, 470·72)	130	263·43 (209·70, 332·70)
Week 24	130	325·48 (257·85, 413·15)	130	409·15 (322·40, 522·26)	130	310·51 (246·25, 393·69)	130	253·31 (201·82, 319·62)
	Adjusted Model							
Week 0	130	372·93 (307·03, 454·73)	130	376·22 (308·72, 460·32)	130	371·80 (305·06, 454·95)	130	373·50 (306·85, 456·40)
Week 4	130	342·25 (282·23, 416·60)	130	386·12 (316·68, 472·67)	130	323·58 (266·22, 394·83)	130	294·30 (242·90, 357·91)
Week 12	130	323·08 (266·72, 392·82)	130	369·47 (303·29, 451·89)	130	348·12 (286·00, 425·40)	130	253·24 (209·61, 307·08)
Week 24	130	321·70 (265·61, 391·11)	130	369·68 (303·46, 452·15)	130	291·76 (240·51, 355·27)	130	243·55 (201·73, 295·10)

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation.

Table S11. P-values for pairwise comparisons between conditions at each time point for urinary total NNAL standardized by creatinine using multiple imputation method

Unadjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·58	..		
8 mg/ml	0·77	0·79	..	
36 mg/ml	0·86	0·70	0·91	..
Week 4				
CS	..			
0 mg/ml	0·50	..		
8 mg/ml	0·79	0·34	..	
36 mg/ml	0·30	0·09	0·44	..
Week 12				
CS	..			
0 mg/ml	0·63	..		
8 mg/ml	0·68	0·94	..	
36 mg/ml	0·11	0·04	0·05	..
Week 24				
CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·24	0·35	..	
36 mg/ml	0·01[S]	0·03	0·26	..
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·98	..		
8 mg/ml	1·00	0·97	..	
36 mg/ml	0·99	0·97	0·99	..
Week 4				
CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·49	0·36	..	
36 mg/ml	0·13	0·09	0·41	..
Week 12				
CS	..			
0 mg/ml	1·00	..		
8 mg/ml	0·86	0·88	..	

36 mg/ml	0·02	0·04	0·03	··
Week 24				
CS	··			
0 mg/ml	0·40	··		
8 mg/ml	0·10	0·40	··	
36 mg/ml	0·0004	0·03	0·24	··

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·008, between all conditions.

S Significant difference at week 24 between CS and 36 mg/ml conditions in unadjusted model with p=0·006.

Table S12. P-values for pairwise comparisons between conditions at each time point for urinary total NNAL standardized by creatinine using intent-to-treat method

Unadjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	··			
0 mg/ml	0·57	··		
8 mg/ml	0·77	0·79	··	
36 mg/ ml	0·86	0·70	0·91	··
Week 4				
CS	··			
0 mg/ml	0·31	··		
8 mg/ml	0·61	0·14	··	
36 mg/ ml	0·34	0·05	0·66	··
Week 12				
CS	··			
0 mg/ml	0·56	··		
8 mg/ml	0·76	0·77	··	
36 mg/ ml	0·19	0·07	0·11	··
Week 24				
CS	··			
0 mg/ml	0·98	··		
8 mg/ml	0·16	0·18	··	
36 mg/ ml	0·06	0·07	0·66	··
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	··			
0 mg/ml	0·96	··		
8 mg/ml	0·96	0·93	··	
36 mg/ ml	0·99	0·97	0·96	··
Week 4				
CS	··			
0 mg/ml	0·44	··		
8 mg/ml	0·50	0·16	··	
36 mg/ ml	0·17	0·04	0·50	··
Week 12				
CS	··			
0 mg/ml	0·77	··		

8 mg/ml	0·67	0·91	··	
36 mg/ml	0·05	0·03	0·02	··
Week 24				
CS	··			
0 mg/ml	0·72	··		
8 mg/ml	0·10	0·23	··	
36 mg/ ml	0·001	0·01	0·15	··

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·008, between all conditions.

Table S13. P-values for pairwise comparisons between conditions at each time point for urinary total NNAL standardized by creatinine using per-protocol method

Unadjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·81	0·98	..	
36 mg/ml	0·32	0·25	0·24	..
Week 4				
CS	..			
0 mg/ml	0·74	..		
8 mg/ml	0·29	0·18	..	
36 mg/ml	0·89	0·65	0·36	..
Week 12				
CS	..			
0 mg/ml	0·73	..		
8 mg/ml	0·92	0·81	..	
36 mg/ml	0·16	0·32	0·22	..
Week 24				
CS	..			
0 mg/ml	0·61	..		
8 mg/ml	0·10	0·29	..	
36 mg/ml	0·05	0·19	0·83	..
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·76	..		
8 mg/ml	0·87	0·89	..	
36 mg/ml	0·70	0·51	0·60	..
Week 4				
CS	..			
0 mg/ml	0·72	..		
8 mg/ml	0·32	0·20	..	
36 mg/ml	0·33	0·20	0·96	..
Week 12				
CS	..			
0 mg/ml	0·64	..		
8 mg/ml	0·94	0·61	..	

36 mg/ml	0·01	0·05	0·02	··
Week 24				
CS	··			
0 mg/ml	0·50	··		
8 mg/ml	0·07	0·28	··	
36 mg/ml	0·002	0·02	0·24	··

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·008, between all conditions.

Table S14. P-values for pairwise comparisons between conditions at each time point for urinary total NNAL standardized by creatinine using baseline-carried-forward method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·57	..		
8 mg/ml	0·77	0·79	..	
36 mg/ml	0·86	0·70	0·91	..
Week 4				
CS	..			
0 mg/ml	0·22	..		
8 mg/ml	0·92	0·19	..	
36 mg/ml	0·47	0·05	0·54	..
Week 12				
CS	..			
0 mg/ml	0·36	..		
8 mg/ml	0·51	0·81	..	
36 mg/ml	0·23	0·04	0·06	..
Week 24				
CS	..			
0 mg/ml	0·62	..		
8 mg/ml	0·61	0·32	..	
36 mg/ml	0·04	0·01	0·12	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·98	..		
8 mg/ml	0·96	0·94	..	
36 mg/ml	0·98	1·00	0·94	..
Week 4				
CS	..			
0 mg/ml	0·34	..		
8 mg/ml	0·63	0·15	..	
36 mg/ml	0·22	0·03	0·45	..
Week 12				
CS	..			
0 mg/ml	0·61	..		
8 mg/ml	0·60	0·99	..	

36 mg/ml	0·06	0·02	0·02	··
Week 24				
CS	··			
0 mg/ml	0·94	··		
8 mg/ml	0·25	0·28	··	
36 mg/ml	0·002	0·002	0·05	··

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0.008, between all conditions.

Table S15. P-values for pairwise comparisons between conditions at each time point for urinary total NNAL standardized by creatinine using last-observation-carried-forward method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·57	..		
8 mg/ml	0·77	0·79	..	
36 mg/ml	0·86	0·70	0·91	..
Week 4				
CS	..			
0 mg/ml	0·22	..		
8 mg/ml	0·92	0·19	..	
36 mg/ml	0·47	0·05	0·54	..
Week 12				
CS	..			
0 mg/ml	0·19	..		
8 mg/ml	0·47	0·56	..	
36 mg/ml	0·20	0·01	0·05	..
Week 24				
CS	..			
0 mg/ml	0·18	..		
8 mg/ml	0·78	0·11	..	
36 mg/ml	0·14	0·01 [S]	0·22	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·95	..		
8 mg/ml	0·98	0·93	..	
36 mg/ml	0·99	0·96	0·97	..
Week 4				
CS	..			
0 mg/ml	0·35	..		
8 mg/ml	0·66	0·17	..	
36 mg/ml	0·24	0·04	0·46	..
Week 12				
CS	..			
0 mg/ml	0·30	..		
8 mg/ml	0·56	0·65	..	

36 mg/ml	0·05	0·003	0·01	··
Week 24				
CS	··			
0 mg/ml	0·28	··		
8 mg/ml	0·44	0·07	··	
36 mg/ml	0·03	0·001	0·15	··

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·008, between all conditions.

S Significant difference at week 24 between 0 mg/ml and 36 mg/ml conditions in unadjusted model with p=0·005, comparing to Bonferroni correction alpha=0·008.

Table S16. P-values for pairwise comparisons relative to baseline within each condition for urinary total NNAL standardized by creatinine using multiple imputation method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·58	0·76	0·18	0·03
Week 12	0·27	0·33	0·35	0·001
Week 24	0·62	0·20	0·06	0·0005
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·57	0·76	0·17	0·02
Week 12	0·21	0·29	0·29	0·0003
Week 24	0·56	0·14	0·04	<0·0001

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S17. P-values for pairwise comparisons relative to baseline within each condition for urinary total NNAL standardized by creatinine using intent-to-treat method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·55	0·89	0·08	0·03
Week 12	0·36	0·48	0·41	0·01
Week 24	0·59	0·33	0·02	0·004
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·48	0·83	0·15	0·02
Week 12	0·25	0·42	0·54	0·0009
Week 24	0·56	0·34	0·02	<0·0001

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S18. P-values for pairwise comparisons relative to baseline within each condition for urinary total NNAL standardized by creatinine using per-protocol method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·53	0·81	0·09	0·02
Week 12	0·55	0·49	0·72	0·0007
Week 24	0·78	0·58	0·09	0·0007
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·53	0·81	0·13	0·02
Week 12	0·52	0·46	0·75	0·0002
Week 24	0·75	0·53	0·06	0·0001

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S19. P-values for pairwise comparisons relative to baseline within each condition for urinary total NNAL standardized by creatinine using baseline-carried-forward method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·41	0·81	0·14	0·02
Week 12	0·33	0·59	0·62	0·01
Week 24	0·76	0·70	0·22	0·004
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·40	0·80	0·18	0·02
Week 12	0·26	0·54	0·60	0·002
Week 24	0·70	0·63	0·13	0·0003

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S20. P-values for pairwise comparisons relative to baseline within each condition for urinary total NNAL standardized by creatinine using last-observation-carried-forward method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·39	0·79	0·12	0·02[S]
Week 12	0·26	0·89	0·58	0·002
Week 24	0·30	0·90	0·09	0·003
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·38	0·79	0·16	0·01
Week 12	0·22	0·88	0·58	0·0007
Week 24	0·23	0·89	0·05	0·0005

Note: NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 cigarettes smoked per day, week 0 forced expiratory volume in one second, and week 0 urinary total NNAL (pg/mg creatinine-transformed).

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

S Significant difference between week 4 and week 0 in 36 mg/ml condition for unadjusted model, p-value=0·015, comparing to Bonferroni correction alpha=0·017.

Table S21. Estimated urinary cotinine standardized by creatinine in unadjusted and adjusted mixed models using multiple imputation method

Cotinine, ng/mg creatinine*	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)
Week 0	130	1441·56 (1186·10, 1752·03)	130	1444·53 (1188·55, 1755·65)	130	1729·53 (1423·04, 2102·03)	130	1658·74 (1364·80, 2015·99)
Week 4	130	1384·71 (1131·96, 1693·90)	130	1290·74 (1053·1, 1582·02)	130	1279·92 (1045·16, 1567·42)	130	1696·03 (1375·86, 2090·70)
Week 12	130	1073·87 (872·92, 1321·08)	130	1266·75 (1020·85, 1571·88)	130	1092·94 (876·82, 1362·31)	130	1313·39 (1051·80, 1640·03)
Week 24	130	1128·08 (904·59, 1406·79)	130	1235·99 (935·55, 1632·91)	130	1157·95 (910·95, 1471·93)	130	1472·99 (1206·13, 1798·90)
	Adjusted Model							
Week 0	130	1499·24 (1246·04, 1803·89)	130	1465·65 (1213·31, 1770·48)	130	1601·43 (1327·57, 1931·79)	130	1589·17 (1318·30, 1915·70)
Week 4	130	1440·12 (1201·22, 1726·53)	130	1309·62 (1072·56, 1599·07)	130	1185·13 (985·38, 1425·37)	130	1624·90 (1305·91, 2021·80)
Week 12	130	1116·84 (911·15, 1368·96)	130	1285·27 (1027·49, 1607·72)	130	1011·99 (825·35, 1240·83)	130	1258·30 (1012·00, 1564·55)
Week 24	130	1173·22 (960·36, 1433·26)	130	1254·06 (966·87, 1626·54)	130	1072·19 (867·98, 1324·45)	130	1411·21 (1167·77, 1705·39)

Note: CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation.

Table S22. Estimated urinary cotinine standardized by creatinine in unadjusted and adjusted mixed models using intent-to-treat method

Cotinine, ng/mg creatinine*	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimated Mean (95% CI)**
Week 0	130	1441·56 (1186·96, 1750·77)	130	1444·53 (1189·41, 1754·38)	130	1729·53 (1424·07, 2100·51)	130	1658·74 (1365·79, 2014·54)
Week 4	115	1393·72 (1136·93, 1708·51)	96	1281·77 (1029·82, 1595·37)	110	1251·12 (1016·94, 1539·22)	111	1742·55 (1417·63, 2141·95)
Week 12	92	1071·05 (856·10, 1339·96)	77	1313·44 (1028·71, 1676·97)	85	1060·89 (841·53, 1337·42)	93	1388·93 (1110·17, 1737·70)
Week 24	90	1134·96 (901·20, 1429·37)	69	1160·71 (893·92, 1507·14)	73	1049·47 (815·68, 1350·27)	79	1516·06 (1188·54, 1933·84)
	Adjusted Model							
Week 0	130	1529·53 (1263·16, 1852·07)	130	1485·39 (1214·60, 1816·55)	130	1661·48 (1361·10, 2028·15)	130	1616·43 (1328·34, 1966·99)
Week 4	115	1502·24 (1229·96, 1834·80)	96	1282·43 (1026·92, 1601·52)	110	1184·99 (959·11, 1464·07)	111	1717·15 (1398·89, 2107·83)
Week 12	92	1127·26 (907·33, 1400·50)	77	1255·50 (982·35, 1604·60)	85	1049·20 (828·37, 1328·9)	93	1344·97 (1078·18, 1677·77)
Week 24	90	1227·72 (984·09, 1531·68)	69	1115·03 (859·67, 1446·23)	73	1010·55 (782·97, 1304·28)	79	1387·57 (1092·64, 1762·11)

Note: CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation.

Table S23. Estimated urinary cotinine standardized by creatinine in unadjusted and adjusted mixed models using per-protocol method

Cotinine, ng/mg creatinine*	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**
Week 0	85	1470·86 (1141·94, 1894·53)	67	1334·90 (1003·76, 1775·28)	66	1604·61 (1203·97, 2138·57)	77	1817·95 (1393·43, 2371·82)
Week 4	85	1413·46 (1097·37, 1820·59)	67	1146·69 (862·24, 1524·98)	66	1190·03 (892·91, 1586·03)	77	1861·07 (1426·47, 2428·07)
Week 12	85	1082·83 (840·68, 1394·72)	67	1190·56 (895·23, 1583·32)	66	1022·50 (767·20, 1362·75)	77	1472·28 (1128·47, 1920·83)
Week 24	85	1152·62 (894·87, 1484·62)	67	1112·04 (836·19, 1478·90)	66	1011·77 (759·15, 1348·45)	77	1559·63 (1195·42, 2034·79)
	Adjusted Model							
Week 0	85	1536·03 (1173·34, 2010·84)	67	1439·00 (1055·21, 1962·39)	66	1693·35 (1238·30, 2315·61)	77	1717·75 (1285·84, 2294·75)
Week 4	85	1478·97 (1129·75, 1936·14)	67	1179·08 (864·61, 1607·92)	66	1213·71 (887·55, 1659·72)	77	1785·17 (1336·31, 2384·81)
Week 12	85	1130·50 (863·56, 1479·95)	67	1174·38 (861·16, 1601·52)	66	1112·99 (813·90, 1521·99)	77	1385·30 (1036·98, 1850·62)
Week 24	85	1219·00 (931·17, 1595·81)	67	1071·96 (786·06, 1461·85)	66	985·59 (720·74, 1347·77)	77	1407·94 (1053·93, 1880·87)

Note: CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score. Sample size included participants who have available urinary cotinine at week 0, 4, 12 and 24, which is N=85, 67, 66 and 77 for CS, 0 mg/ml, 8 mg/ml and 36 mg/ml, respectively.

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation.

Table S24. Estimated urinary cotinine standardized by creatinine in unadjusted and adjusted mixed models using baseline-carried-forward method

Cotinine, ng/mg creatinine*	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**	**N**	**Estimates (95% CI)**
Week 0	130	1441·56 (1195·26, 1738·61)	130	1444·53 (1197·72, 1742·2)	130	1729·53 (1434·03, 2085·92)	130	1658·74 (1375·34, 2000·55)
Week 4	130	1401·16 (1161·77, 1689·89)	130	1305·99 (1082·85, 1575·10)	130	1321·16 (1095·43, 1593·40)	130	1707·43 (1415·70, 2059·26)
Week 12	130	1147·16 (951·16, 1383·54)	130	1331·27 (1103·82, 1605·60)	130	1268·79 (1052·01, 1530·24)	130	1413·43 (1171·94, 1704·69)
Week 24	130	1226·91 (1017·28, 1479·73)	130	1311·50 (1087·43, 1581·76)	130	1362·23 (1129·48, 1642·93)	130	1518·93 (1259·41, 1831·93)
	Adjusted Model							
Week 0	130	1521·17 (1284·69, 1801·17)	130	1484·15 (1242·92, 1772·21)	130	1620·63 (1359·07, 1932·53)	130	1593·01 (1339·56, 1894·41)
Week 4	130	1492·57 (1260·54, 1767·31)	130	1327·73 (1111·92, 1585·42)	130	1212·99 (1017·22, 1446·43)	130	1668·30 (1402·88, 1983·95)
Week 12	130	1210·39 (1022·23, 1433·19)	130	1322·03 (1107·15, 1578·61)	130	1204·19 (1009·84, 1435·94)	130	1372·06 (1153·77, 1631·66)
Week 24	130	1307·15 (1103·95, 1547·76)	130	1273·64 (1066·62, 1520·83)	130	1247·33 (1046·01, 1487·38)	130	1418·98 (1193·22, 1687·45)

Note: CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation.

Table S25. Estimated urinary cotinine standardized by creatinine in unadjusted and adjusted mixed models using last-observation-carried-forward method

Cotinine, ng/mg creatinine*	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)	N	Estimates (95% CI)
Week 0	130	1441·56 (1194·16, 1740·21)	130	1444·53 (1196·63, 1743·79)	130	1729·53 (1432·71, 2087·83)	130	1658·74 (1374·08, 2002·38)
Week 4	130	1401·16 (1160·70, 1691·44)	130	1305·99 (1081·86, 1576·55)	130	1321·16 (1094·43, 1594·86)	130	1707·43 (1414·41, 2061·15)
Week 12	130	1143·42 (947·19, 1380·30)	130	1343·97 (1113·32, 1622·40)	130	1173·91 (972·44, 1417·10)	130	1422·59 (1178·45, 1717·31)
Week 24	130	1181·58 (978·80, 1426·36)	130	1302·10 (1078·64, 1571·86)	130	1154·63 (956·48, 1393·83)	130	1474·60 (1221·53, 1780·09)
	Adjusted Model							
Week 0	130	1516·94 (1268·82, 1813·59)	130	1474·78 (1222·33, 1779·36)	130	1642·33 (1363·41, 1978·32)	130	1595·93 (1328·43, 1917·3)
Week 4	130	1488·43 (1244·97, 1779·5)	130	1319·34 (1093·50, 1591·81)	130	1229·23 (1020·46, 1480·70)	130	1671·36 (1391·22, 2007·92)
Week 12	130	1212·61 (1014·26, 1449·74)	130	1334·72 (1106·25, 1610·37)	130	1116·24 (926·66, 1344·59)	130	1384·31 (1152·28, 1663·06)
Week 24	130	1262·43 (1055·94, 1509·31)	130	1275·75 (1057·37, 1539·22)	130	1055·46 (876·20, 1271·38)	130	1400·47 (1165·73, 1682·48)

Note: CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Estimates with 95% confidence intervals were obtained via back-transformation to the original scale following Box-Cox transformation and multiple imputation.

Table S26. P-values for pairwise comparisons between conditions at each time point for urinary cotinine standardized by creatinine using multiple imputation method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·99	..		
8 mg/ml	0·20	0·20	..	
36 mg/ml	0·32	0·33	0·77	..
Week 4				
CS	..			
0 mg/ml	0·64	..		
8 mg/ml	0·58	0·95	..	
36 mg/ml	0·19	0·07	0·07	..
Week 12				
CS	..			
0 mg/ml	0·28	..		
8 mg/ml	0·91	0·37	..	
36 mg/ml	0·17	0·82	0·29	..
Week 24				
CS	..			
0 mg/ml	0·64	..		
8 mg/ml	0·88	0·67	..	
36 mg/ml	0·07	0·34	0·15	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·85	..		
8 mg/ml	0·58	0·46	..	
36 mg/ml	0·62	0·50	0·95	..
Week 4				
CS	..			
0 mg/ml	0·46	..		
8 mg/ml	0·11	0·44	..	
36 mg/ml	0·37	0·10	0·02	..
Week 12				
CS	..			
0 mg/ml	0·28	..		
8 mg/ml	0·47	0·10	..	

36 mg/ml	0·35	0·88	0·17	··
Week 24				
CS	··			
0 mg/ml	0·72	··		
8 mg/ml	0·56	0·25	··	
36 mg/ml	0·15	0·49	0·07	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·008, between all conditions.

Table S27. P-values for pairwise comparisons between conditions at each time point for urinary cotinine standardized by creatinine using intent-to-treat method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·99	..		
8 mg/ml	0·19	0·20	..	
36 mg/ml	0·32	0·32	0·77	..
Week 4				
CS	..			
0 mg/ml	0·58	..		
8 mg/ml	0·47	0·87	..	
36 mg/ml	0·13	0·05	0·03	..
Week 12				
CS	..			
0 mg/ml	0·23	..		
8 mg/ml	0·95	0·21	..	
36 mg/ml	0·11	0·74	0·10	..
Week 24				
CS	..			
0 mg/ml	0·90	..		
8 mg/ml	0·65	0·59	..	
36 mg/ml	0·09	0·14	0·04	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·82	..		
8 mg/ml	0·51	0·39	..	
36 mg/ml	0·66	0·51	0·83	..
Week 4				
CS	..			
0 mg/ml	0·25	..		
8 mg/ml	0·08	0·58	..	
36 mg/ml	0·31	0·04	0·01[S]	..
Week 12				
CS	..			
0 mg/ml	0·49	..		
8 mg/ml	0·64	0·27	..	

36 mg/ml	0·22	0·66	0·10	··
Week 24				
CS	··			
0 mg/ml	0·55	··		
8 mg/ml	0·23	0·57	··	
36 mg/ml	0·42	0·19	0·06	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·008, between all conditions.

S Significant difference between 8 mg/ml and 36 mg/ml at week 4 in adjusted model, p-value=0·006, comparing to Bonferroni correction alpha=0·008.

Table S28. P-values for pairwise comparisons between conditions at each time point for urinary cotinine standardized by creatinine using per-protocol method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·62	..		
8 mg/ml	0·66	0·37	..	
36 mg/ml	0·26	0·12	0·53	..
Week 4				
CS	..			
0 mg/ml	0·28	..		
8 mg/ml	0·38	0·86	..	
36 mg/ml	0·14	0·02	0·03	..
Week 12				
CS	..			
0 mg/ml	0·63	..		
8 mg/ml	0·77	0·46	..	
36 mg/ml	0·10	0·29	0·07	..
Week 24				
CS	..			
0 mg/ml	0·85	..		
8 mg/ml	0·50	0·65	..	
36 mg/ml	0·11	0·09	0·03	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·72	..		
8 mg/ml	0·61	0·42	..	
36 mg/ml	0·52	0·35	0·94	..
Week 4				
CS	..			
0 mg/ml	0·22	..		
8 mg/ml	0·29	0·89	..	
36 mg/ml	0·28	0·03	0·05	..
Week 12				
CS	..			
0 mg/ml	0·84	..		
8 mg/ml	0·93	0·79	..	

36 mg/ml	0·25	0·38	0·26	··
Week 24				
CS	··			
0 mg/ml	0·49	··		
8 mg/ml	0·26	0·68	··	
36 mg/ml	0·41	0·15	0·06	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·008, between all conditions.

Table S29. P-values for pairwise comparisons between conditions at each time point for urinary cotinine standardized by creatinine using baseline-carried-forward method

Unadjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·99	..		
8 mg/ml	0·18	0·18	..	
36 mg/ml	0·30	0·31	0·76	..
Week 4				
CS	..			
0 mg/ml	0·60	..		
8 mg/ml	0·66	0·93	..	
36 mg/ml	0·14	0·05	0·06	..
Week 12				
CS	..			
0 mg/ml	0·27	..		
8 mg/ml	0·46	0·72	..	
36 mg/ml	0·12	0·66	0·42	..
Week 24				
CS	..			
0 mg/ml	0·62	..		
8 mg/ml	0·44	0·78	..	
36 mg/ml	0·11	0·28	0·42	..
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·58	0·45	..	
36 mg/ml	0·68	0·53	0·88	..
Week 4				
CS	..			
0 mg/ml	0·30	..		
8 mg/ml	0·07	0·43	..	
36 mg/ml	0·32	0·05	0·01[S]	..
Week 12				
CS	..			
0 mg/ml	0·43	..		
8 mg/ml	0·96	0·42	..	

36 mg/ml	0·26	0·74	0·25	··
Week 24				
CS	··			
0 mg/ml	0·82	··		
8 mg/ml	0·68	0·86	··	
36 mg/ml	0·46	0·34	0·26	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·008, between all conditions.

S Significant difference between 8 mg/ml and 36 mg/ml at week 4 in adjusted model, p-value=0·005, comparing to Bonferroni correction alpha=0·008.

Table S30. P-values for pairwise comparisons between conditions at each time point for urinary cotinine standardized by creatinine using last-observation-carried-forward method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·99	..		
8 mg/ml	0·18	0·19	..	
36 mg/ml	0·30	0·31	0·76	..
Week 4				
CS	..			
0 mg/ml	0·60	..		
8 mg/ml	0·67	0·93	..	
36 mg/ml	0·15	0·05	0·06	..
Week 12				
CS	..			
0 mg/ml	0·23	..		
8 mg/ml	0·85	0·32	..	
36 mg/ml	0·11	0·68	0·16	..
Week 24				
CS	..			
0 mg/ml	0·47	..		
8 mg/ml	0·87	0·38	..	
36 mg/ml	0·10	0·36	0·07	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·81	..		
8 mg/ml	0·50	0·37	..	
36 mg/ml	0·66	0·51	0·81	..
Week 4				
CS	..			
0 mg/ml	0·31	..		
8 mg/ml	0·11	0·56	..	
36 mg/ml	0·32	0·05	0·01	..
Week 12				
CS	..			
0 mg/ml	0·42	..		
8 mg/ml	0·48	0·14	..	

36 mg/ml	0·25	0·76	0·07	··
Week 24				
CS	··			
0 mg/ml	0·93	··		
8 mg/ml	0·13	0·12	··	
36 mg/ml	0·37	0·43	0·02	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·008, between all conditions.

Table S31. P-values for pairwise comparisons relative to baseline within each condition for urinary cotinine standardized by creatinine using multiple imputation method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·71	0·30	0·01	0·84
Week 12	0·02	0·33	0·001	0·09
Week 24	0·09	0·36	0·01	0·38
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·70	0·29	0·01	0·84
Week 12	0·02[S]	0·29	0·0004	0·07
Week 24	0·06	0·33	0·01	0·32

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

***** Bonferroni correction alpha=0·017, relative to baseline (week 0).

S Significant difference between week 12 and week 0 in cigarette substitute condition for adjusted model, p-value=0·015, comparing to Bonferroni correction alpha=0·017.

Table S32. P-values for pairwise comparisons relative to baseline within each condition for urinary cotinine standardized by creatinine using intent-to-treat method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·75	0·29	0·003	0·64
Week 12	0·03	0·51	0·0004	0·19
Week 24	0·10	0·17	0·001	0·55
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·86	0·20	0·002	0·57
Week 12	0·02	0·23	0·0008	0·15
Week 24	0·10	0·06	0·0009	0·28

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S33. P-values for pairwise comparisons relative to baseline within each condition for urinary cotinine standardized by creatinine using per-protocol method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·76	0·30	0·05	0·86
Week 12	0·06	0·52	0·01	0·21
Week 24	0·16	0·35	0·02	0·40
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·78	0·20	0·04	0·79
Week 12	0·05	0·26	0·03	0·19
Week 24	0·16	0·12	0·01	0·25

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S34. P-values for pairwise comparisons relative to baseline within each condition for urinary cotinine standardized by creatinine using baseline-carried-forward method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·75	0·26	0·003	0·75
Week 12	0·04	0·46	0·01	0·15
Week 24	0·19	0·43	0·05	0·47
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 4	0·83	0·23	0·002	0·61
Week 12	0·03	0·28	0·01	0·16
Week 24	0·16	0·17	0·02	0·29

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S35. P-values for pairwise comparisons relative to baseline within each condition for urinary cotinine standardized by creatinine using last-observation-carried-forward method

Unadjusted Model*				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 4	0·74	0·24	0·002	0·73
Week 12	0·03	0·50	0·0003	0·15
Week 24	0·10	0·39	0·0007	0·33
Adjusted Model*				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 4	0·83	0·21	0·001	0·60
Week 12	0·03	0·35	0·0003	0·17
Week 24	0·10	0·20	0·0001	0·24

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 urinary cotinine (ng/mg creatinine-transformed), education level, week 0 environmental smoke score, week 0 partial INTERHEART non-laboratory score, week 0 forced expiratory volume in one second, week 0 forced vital capacity, and week 0 Penn State Cigarette Dependence Index score.

* Bonferroni correction alpha=0·017, relative to baseline (week 0).

Table S36. Estimated mean exhaled carbon monoxide in unadjusted and adjusted mixed models using multiple imputation method

CO, parts per million	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)
Week 0	130	23·65 (21·76, 25·53)	130	23·35 (21·47, 25·24)	130	21·84 (19·95, 23·73)	130	21·94 (20·05, 23·83)
Week 1	130	21·36 (19·45, 23·27)	130	21·00 (18·98, 23·01)	130	16·20 (14·26, 18·13)	130	17·69 (15·79, 19·58)
Week 2	130	21·12 (19·12, 23·12)	130	19·91 (17·76, 22·06)	130	15·86 (13·88, 17·85)	130	17·39 (15·47, 19·31)
Week 4	130	20·37 (18·32, 22·41)	130	19·97 (18·04, 21·90)	130	15·78 (13·79, 17·76)	130	15·67 (13·67, 17·67)
Week 8	130	20·98 (19·01, 22·94)	130	19·88 (17·55, 22·21)	130	16·19 (14·12, 18·26)	130	16·44 (14·51, 18·38)
Week 12	130	20·05 (17·82, 22·27)	130	21·29 (19·04, 23·53)	130	16·64 (14·65, 18·63)	130	16·55 (14·50, 18·60)
Week 16	130	21·81 (19·85, 23·77)	130	21·87 (19·76, 23·99)	130	16·50 (14·40, 18·59)	130	17·15 (15·04, 19·26)
Week 20	130	20·71 (18·78, 22·65)	130	21·02 (18·74, 23·29)	130	16·56 (14·21, 18·91)	130	15·34 (13·34, 17·34)
Week 24	130	20·79 (18·67, 22·90)	130	21·31 (19·27, 23·36)	130	17·56 (15·09, 20·02)	130	16·93 (14·50, 19·35)
	Adjusted Model							
Week 0	130	23·82 (22·23, 25·41)	130	23·33 (21·73, 24·93)	130	22·87 (21·25, 24·49)	130	22·95 (21·37, 24·54)
Week 1	130	21·53 (19·94, 23·12)	130	20·97 (19·12, 22·81)	130	17·23 (15·52, 18·94)	130	18·70 (17·11, 20·29)
Week 2	130	21·29 (19·61, 22·97)	130	19·88 (17·9, 21·86)	130	16·90 (15·15, 18·64)	130	18·40 (16·74, 20·07)
Week 4	130	20·54 (18·87, 22·21)	130	19·94 (18·32, 21·57)	130	16·81 (15·08, 18·53)	130	16·68 (15·03, 18·34)
Week 8	130	21·15 (19·47, 22·82)	130	19·86 (17·74, 21·97)	130	17·22 (15·56, 18·89)	130	17·46 (15·78, 19·13)
Week 12	130	20·22 (18·24, 22·20)	130	21·26 (19·18, 23·34)	130	17·67 (15·95, 19·39)	130	17·56 (15·79, 19·34)
Week 16	130	21·98 (20·39, 23·57)	130	21·85 (19·86, 23·84)	130	17·53 (15·73, 19·32)	130	18·17 (16·24, 20·10)
Week 20	130	20·88 (19·22, 22·55)	130	20·99 (18·88, 23·1)	130	17·59 (15·54, 19·64)	130	16·36 (14·56, 18·16)
Week 24	130	20·96 (18·95, 22·96)	130	21·29 (19·55, 23·02)	130	18·59 (16·14, 21·03)	130	17·94 (15·6, 20·28)

Note: CO, carbon monoxide; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S37. Estimated mean exhaled carbon monoxide in unadjusted and adjusted mixed models using intent-to-treat method

CO, parts per million	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**
Week 0	130	23·65 (21·73, 25·56)	130	23·35 (21·44, 25·27)	130	21·84 (19·92, 23·76)	130	21·94 (20·02, 23·86)
Week 1	121	21·2 (19·25, 23·16)	112	20·78 (18·78, 22·78)	116	16·16 (14·18, 18·13)	120	17·74 (15·78, 19·69)
Week 2	115	21·06 (19·07, 23·05)	103	20·14 (18·07, 22·21)	116	15·75 (13·76, 17·74)	112	17·16 (15·15, 19·17)
Week 4	115	19·89 (17·88, 21·90)	96	19·64 (17·49, 21·78)	109	15·79 (13·74, 17·83)	112	15·39 (13·36, 17·42)
Week 8	95	21·03 (18·90, 23·16)	84	19·28 (17·00, 21·56)	92	15·98 (13·81, 18·15)	95	16·31 (14·17, 18·45)
Week 12	91	19·74 (17·54, 21·94)	77	20·99 (18·60, 23·38)	85	16·57 (14·31, 18·84)	93	16·38 (14·18, 18·58)
Week 16	85	21·71 (19·43, 23·99)	71	21·60 (19·11, 24·10)	77	16·18 (13·81, 18·54)	84	16·96 (14·66, 19·26)
Week 20	86	20·87 (18·57, 23·18)	65	20·59 (18·00, 23·18)	72	16·10 (13·64, 18·56)	78	14·87 (12·48, 17·26)
Week 24	91	20·38 (18·10, 22·66)	69	19·47 (16·88, 22·06)	74	17·45 (14·96, 19·95)	80	16·41 (13·99, 18·82)
	Adjusted Model							
Week 0	130	23·70 (22·04, 25·36)	130	22·97 (21·22, 24·71)	130	22·92 (21·19, 24·66)	130	22·80 (21·12, 24·48)
Week 1	121	21·13 (19·43, 22·82)	112	19·59 (17·76, 21·41)	116	17·22 (15·43, 19·02)	120	18·56 (16·84, 20·27)
Week 2	115	21·31 (19·58, 23·05)	103	18·95 (17·06, 20·85)	116	16·43 (14·63, 18·24)	112	17·74 (15·98, 19·49)
Week 4	115	20·49 (18·74, 22·23)	96	18·95 (16·99, 20·90)	109	16·47 (14·62, 18·32)	112	16·37 (14·61, 18·14)
Week 8	95	21·07 (19·21, 22·93)	84	19·24 (17·17, 21·31)	92	17·17 (15·18, 19·16)	95	16·95 (15·06, 18·83)
Week 12	91	20·20 (18·29, 22·10)	77	21·56 (19·41, 23·71)	85	17·39 (15·30, 19·48)	93	17·17 (15·26, 19·09)
Week 16	85	22·50 (20·54, 24·46)	71	22·01 (19·77, 24·25)	77	17·27 (15·09, 19·44)	84	17·17 (15·16, 19·17)
Week 20	86	20·91 (18·93, 22·88)	65	21·15 (18·83, 23·47)	72	17·25 (15·02, 19·48)	78	14·98 (12·90, 17·06)
Week 24	91	20·50 (18·56, 22·43)	69	19·62 (17·33, 21·92)	74	18·78 (16·53, 21·02)	80	16·72 (14·64, 18·79)

Note: CO, carbon monoxide; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S38. Estimated mean exhaled carbon monoxide in unadjusted and adjusted mixed models using per-protocol method

CO, parts per million	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**
Week 0	85	23·74 (21·37, 26·11)	67	21·10 (18·44, 23·77)	67	21·87 (19·20, 24·53)	79	21·77 (19·32, 24·23)
Week 1	83	21·66 (19·28, 24·04)	65	19·19 (16·51, 21·88)	64	15·44 (12·74, 18·13)	78	18·49 (16·03, 20·95)
Week 2	83	21·85 (19·47, 24·23)	65	19·19 (16·50, 21·88)	67	15·22 (12·56, 17·89)	77	17·28 (14·81, 19·74)
Week 4	85	20·18 (17·81, 22·54)	67	18·72 (16·05, 21·38)	67	14·61 (11·95, 17·28)	79	14·97 (12·52, 17·43)
Week 8	79	21·29 (18·89, 23·70)	66	18·28 (15·60, 20·95)	66	15·52 (12·85, 18·20)	75	15·34 (12·86, 17·83)
Week 12	85	19·81 (17·44, 22·18)	67	20·60 (17·93, 23·26)	67	16·06 (13·39, 18·73)	79	15·24 (12·78, 17·70)
Week 16	79	21·61 (19·20, 24·02)	64	20·93 (18·24, 23·62)	63	15·65 (12·94, 18·35)	77	15·04 (12·57, 17·51)
Week 20	80	21·14 (18·73, 23·54)	61	20·33 (17·61, 23·05)	65	16·16 (13·47, 18·84)	77	13·62 (11·15, 16·09)
Week 24	85	20·81 (18·44, 23·18)	67	19·30 (16·63, 21·97)	67	17·52 (14·86, 20·19)	79	15·58 (13·13, 18·04)
	Adjusted Model							
Week 0	85	23·22 (21·07, 25·37)	67	21·51 (19·02, 24·00)	67	22·58 (20·07, 25·09)	79	22·78 (20·53, 25·02)
Week 1	83	20·99 (18·84, 23·15)	65	18·66 (16·15, 21·18)	64	16·02 (13·47, 18·57)	78	19·47 (17·21, 21·72)
Week 2	83	21·37 (19·21, 23·54)	65	18·61 (16·10, 21·13)	67	15·51 (13·00, 18·02)	77	18·04 (15·78, 20·31)
Week 4	85	19·99 (17·84, 22·14)	67	18·70 (16·21, 21·19)	67	14·94 (12·44, 17·45)	79	15·91 (13·67, 18·16)
Week 8	79	20·76 (18·56, 22·96)	66	18·61 (16·11, 21·11)	66	16·66 (14·14, 19·18)	75	16·23 (13·95, 18·50)
Week 12	85	19·74 (17·59, 21·89)	67	21·11 (18·62, 23·60)	67	17·05 (14·55, 19·56)	79	16·13 (13·89, 18·38)
Week 16	79	21·94 (19·75, 24·13)	64	21·30 (18·79, 23·81)	63	16·52 (13·97, 19·07)	77	15·89 (13·63, 18·16)
Week 20	80	20·75 (18·56, 22·94)	61	20·52 (17·97, 23·07)	65	17·23 (14·71, 19·75)	77	14·24 (11·98, 16·50)
Week 24	85	20·60 (18·45, 22·75)	67	19·15 (16·66, 21·63)	67	18·65 (16·15, 21·16)	79	16·20 (13·96, 18·45)

Note: CS, cigarette substitute; CO, carbon monoxide; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Sample size included participants who have available carbon monoxide at week 0, 4, 12 and 24, which is N=85, 67, 67 and 79 for CS, 0 mg/ml, 8 mg/ml and 36 mg/ml, respectively.

Table S39. Estimated mean exhaled carbon monoxide in unadjusted and adjusted mixed models using baseline-carried-forward method

CO, parts per million	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**
Week 0	130	23·65 (21·67, 25·62)	130	23·35 (21·38, 25·33)	130	21·84 (19·87, 23·81)	130	21·94 (19·97, 23·91)
Week 1	130	21·49 (19·52, 23·46)	130	20·98 (19·01, 22·96)	130	16·67 (14·70, 18·64)	130	17·93 (15·96, 19·90)
Week 2	130	21·59 (19·62, 23·56)	130	20·71 (18·74, 22·68)	130	16·45 (14·47, 18·42)	130	17·54 (15·57, 19·51)
Week 4	130	20·96 (18·99, 22·93)	130	21·23 (19·26, 23·2)	130	16·75 (14·78, 18·73)	130	15·88 (13·91, 17·86)
Week 8	130	21·55 (19·57, 23·52)	130	21·15 (19·18, 23·13)	130	17·51 (15·54, 19·48)	130	17·13 (15·16, 19·10)
Week 12	130	21·06 (19·09, 23·03)	130	23·00 (21·03, 24·97)	130	18·12 (16·15, 20·09)	130	17·58 (15·61, 19·56)
Week 16	130	23·07 (21·10, 25·04)	130	23·55 (21·57, 25·52)	130	18·07 (16·10, 20·04)	130	18·43 (16·46, 20·40)
Week 20	130	22·18 (20·21, 24·16)	130	23·04 (21·07, 25·01)	130	18·35 (16·37, 20·32)	130	16·92 (14·95, 18·89)
Week 24	130	21·38 (19·41, 23·35)	130	22·46 (20·49, 24·43)	130	19·12 (17·15, 21·09)	130	18·09 (16·12, 20·06)
	Adjusted Model							
Week 0	130	23·69 (22·17, 25·2)	130	23·06 (21·47, 24·66)	130	23·09 (21·51, 24·67)	130	23·05 (21·52, 24·58)
Week 1	130	21·39 (19·87, 22·90)	130	20·07 (18·48, 21·66)	130	17·93 (16·35, 19·52)	130	18·97 (17·44, 20·50)
Week 2	130	21·68 (20·16, 23·20)	130	19·86 (18·26, 21·45)	130	17·26 (15·68, 18·84)	130	18·38 (16·85, 19·91)
Week 4	130	21·24 (19·72, 22·75)	130	20·41 (18·82, 22·01)	130	17·59 (16·01, 19·17)	130	17·05 (15·52, 18·58)
Week 8	130	21·61 (20·09, 23·12)	130	20·85 (19·25, 22·44)	130	18·97 (17·39, 20·55)	130	18·19 (16·66, 19·73)
Week 12	130	21·42 (19·9, 22·93)	130	22·93 (21·34, 24·52)	130	19·38 (17·80, 20·96)	130	18·76 (17·23, 20·29)
Week 16	130	23·37 (21·85, 24·89)	130	23·04 (21·44, 24·63)	130	19·56 (17·98, 21·14)	130	19·18 (17·65, 20·71)
Week 20	130	22·30 (20·79, 23·82)	130	22·82 (21·23, 24·41)	130	19·77 (18·19, 21·35)	130	17·80 (16·27, 19·33)
Week 24	130	21·61 (20·10, 23·13)	130	21·79 (20·20, 23·38)	130	20·59 (19·01, 22·17)	130	18·96 (17·43, 20·49)

Note: CO, carbon monoxide; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S40. Estimated mean exhaled carbon monoxide in unadjusted and adjusted mixed models using last-observation-carried-forward method

CO, parts per million	Unadjusted Model							
Condition	**CS**		**0 mg/ml**		**8 mg/ml**		**36 mg/ml**	
Week	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**	**N**	**Estimated Mean (95% CI)**
Week 0	130	23·65 (21·72, 25·57)	130	23·35 (21·43, 25·28)	130	21·84 (19·91, 23·76)	130	21·94 (20·01, 23·86)
Week 1	130	21·49 (19·57, 23·42)	130	20·98 (19·06, 22·91)	130	16·67 (14·74, 18·59)	130	17·93 (16·01, 19·86)
Week 2	130	21·32 (19·39, 23·24)	130	20·28 (18·36, 22·21)	130	16·07 (14·14, 17·99)	130	17·40 (15·48, 19·32)
Week 4	130	20·32 (18·39, 22·24)	130	20·41 (18·48, 22·33)	130	16·23 (14·31, 18·16)	130	15·82 (13·89, 17·74)
Week 8	130	20·95 (19·02, 22·87)	130	20·42 (18·50, 22·35)	130	16·47 (14·54, 18·39)	130	16·25 (14·33, 18·18)
Week 12	130	19·97 (18·04, 21·89)	130	21·57 (19·64, 23·49)	130	16·92 (14·99, 18·84)	130	16·62 (14·70, 18·55)
Week 16	130	21·29 (19·37, 23·22)	130	22·29 (20·37, 24·22)	130	16·73 (14·81, 18·66)	130	17·21 (15·28, 19·13)
Week 20	130	20·80 (18·88, 22·72)	130	21·94 (20·01, 23·86)	130	16·74 (14·81, 18·66)	130	16·45 (14·52, 18·37)
Week 24	130	20·27 (18·34, 22·19)	130	21·38 (19·46, 23·31)	130	17·48 (15·55, 19·40)	130	17·56 (15·64, 19·49)
	Adjusted Model							
Week 0	130	23·95 (22·32, 25·58)	130	23·30 (21·58, 25·01)	130	23·25 (21·55, 24·95)	130	23·07 (21·43, 24·72)
Week 1	130	21·64 (20·01, 23·27)	130	20·31 (18·59, 22·02)	130	18·09 (16·40, 19·79)	130	18·99 (17·34, 20·64)
Week 2	130	21·64 (20·01, 23·27)	130	19·54 (17·83, 21·25)	130	17·02 (15·33, 18·72)	130	18·29 (16·64, 19·94)
Week 4	130	20·81 (19·18, 22·44)	130	19·79 (18·08, 21·51)	130	17·07 (15·37, 18·76)	130	17·04 (15·39, 18·69)
Week 8	130	21·24 (19·61, 22·87)	130	20·13 (18·41, 21·84)	130	17·71 (16·02, 19·41)	130	17·31 (15·66, 18·95)
Week 12	130	20·53 (18·90, 22·16)	130	21·42 (19·71, 23·14)	130	17·92 (16·23, 19·62)	130	17·78 (16·14, 19·43)
Week 16	130	22·03 (20·40, 23·66)	130	21·85 (20·13, 23·56)	130	18·08 (16·38, 19·77)	130	17·92 (16·27, 19·56)
Week 20	130	21·1 (19·47, 22·73)	130	21·37 (19·66, 23·08)	130	18·10 (16·41, 19·80)	130	17·03 (15·39, 18·68)
Week 24	130	20·71 (19·08, 22·34)	130	20·61 (18·90, 22·32)	130	18·83 (17·13, 20·53)	130	18·13 (16·49, 19·78)

Note: CO, carbon monoxide; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S41. P-values for pairwise comparisons between conditions at each time point for exhaled carbon monoxide using multiple imputation method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·18	0·27	..	
36 mg/ml	0·21	0·30	0·94	..
Week 1				
CS	..			
0 mg/ml	0·80	..		
8 mg/ml	0·0002	0·0006	..	
36 mg/ml	0·01[S]	0·02	0·28	..
Week 2				
CS	..			
0 mg/ml	0·45	..		
8 mg/ml	0·0002	0·01[S]	..	
36 mg/ml	0·01	0·09	0·29	..
Week 4				
CS	..			
0 mg/ml	0·79	..		
8 mg/ml	0·001	0·004	..	
36 mg/ml	0·001	0·003	0·94	..
Week 8				
CS	..			
0 mg/ml	0·48	..		
8 mg/ml	0·001	0·02	..	
36 mg/ml	0·001	0·02	0·86	..
Week 12				
CS	..			
0 mg/ml	0·49	..		
8 mg/ml	0·03	0·004	..	
36 mg/ml	0·03	0·002	0·95	..
Week 16				
CS	..			
0 mg/ml	0·96	..		
8 mg/ml	0·0002	0·0004	..	
36 mg/ml	0·003	0·0006	0·65	..
Week 20				

CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·01[S]	0·003	..	
36 mg/ml	0·0001	0·0001	0·44	..
Week 24				
CS	..			
0 mg/ml	0·73	..		
8 mg/ml	0·03	0·02	..	
36 mg/ml	0·01[S]	0·01[S]	0·67	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·64	..		
8 mg/ml	0·37	0·67	..	
36 mg/ml	0·42	0·73	0·94	..
Week 1				
CS	..			
0 mg/ml	0·62	..		
8 mg/ml	0·0001	0·0007	..	
36 mg/ml	0·01	0·04	0·18	..
Week 2				
CS	..			
0 mg/ml	0·30	..		
8 mg/ml	0·0001	0·02	..	
36 mg/ml	0·01	0·22	0·19	..
Week 4				
CS	..			
0 mg/ml	0·61	..		
8 mg/ml	0·001	0·01[S]	..	
36 mg/ml	0·001	0·01[S]	0·92	..
Week 8				
CS	..			
0 mg/ml	0·32	..		
8 mg/ml	0·001	0·05	..	
36 mg/ml	0·0007	0·05	0·84	..
Week 12				
CS	..			
0 mg/ml	0·52	..		

8 mg/ml	0·06	0·01	··	
36 mg/ml	0·06	0·004	0·92	··
Week 16				
CS	··			
0 mg/ml	0·92	··		
8 mg/ml	0·0002	0·0007	··	
36 mg/ml	0·003	0·0008	0·58	··
Week 20				
CS	··			
0 mg/ml	0·93	··		
8 mg/ml	0·01	0·01[S]	··	
36 mg/ml	<0·0001	0·0002	0·35	··
Week 24				
CS	··			
0 mg/ml	0·80	··		
8 mg/ml	0·06	0·05	··	
36 mg/ml	0·01[S]	0·02	0·59	··

Note: CS, cigarette substitute; CO, carbon monoxide. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

***** Bonferroni correction alpha=0.008, between all conditions.

S Significant difference between cigarette substitute and 36 mg/ml at week 1 for unadjusted model with p=0·007; significant difference between 0 mg/ml and 8 mg/ml at week 2 for unadjusted model with p=0·006; significant difference between cigarette substitute and 8 mg/ml at week 20 for unadjusted model with p=0·0082; significant difference between cigarette substitute and 36 mg/ml at week 24 for unadjusted model with p=0·007; significant difference between 0 mg/ml and 36 mg/ml at week 24 for unadjusted model with p=0·0075; significant difference between 0 mg/ml and 8 mg/ml at week 4 for adjusted model with p=0·0077; significant difference between 0 mg/ml and 36 mg/ml at week 4 for adjusted model with p=0·005; significant difference between 0 mg/ml and 8 mg/ml at week 20 for adjusted model with p=0·006; significant difference between cigarette substitute and 36 mg/ml at week 24 for adjusted model with p=0·00825. All compared to Bonferroni correction alpha=0·05/6=0·00833.

Table S42. P-values for pairwise comparisons between conditions at each time point for exhaled carbon monoxide using intent-to-treat method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·19	0·27	..	
36 mg/ml	0·22	0·31	0·94	..
Week 1				
CS	..			
0 mg/ml	0·77	..		
8 mg/ml	0·0004	0·001	..	
36 mg/ml	0·01	0·03	0·27	..
Week 2				
CS	..			
0 mg/ml	0·53	..		
8 mg/ml	0·0002	0·003	..	
36 mg/ml	0·01[S]	0·04	0·33	..
Week 4				
CS	..			
0 mg/ml	0·86	..		
8 mg/ml	0·01[S]	0·01	..	
36 mg/ml	0·002	0·01[S]	0·79	..
Week 8				
CS	..			
0 mg/ml	0·27	..		
8 mg/ml	0·001	0·04	..	
36 mg/ml	0·002	0·06	0·83	..
Week 12				
CS	..			
0 mg/ml	0·45	..		
8 mg/ml	0·05	0·01	..	
36 mg/ml	0·03	0·01[S]	0·90	..
Week 16				
CS	..			
0 mg/ml	0·95	..		
8 mg/ml	0·001	0·002	..	
36 mg/ml	0·004	0·01[S]	0·64	..
Week 20				

CS	..			
0 mg/ml	0·87	..		
8 mg/ml	0·01[S]	0·01	..	
36 mg/ml	0·0004	0·001	0·48	..
Week 24				
CS	..			
0 mg/ml	0·61	..		
8 mg/ml	0·09	0·27	..	
36 mg/ml	0·02	0·09	0·55	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·51	..		
8 mg/ml	0·49	0·97	..	
36 mg/ml	0·41	0·88	0·91	..
Week 1				
CS	..			
0 mg/ml	0·19	..		
8 mg/ml	0·0008	0·05	..	
36 mg/ml	0·02	0·38	0·25	..
Week 2				
CS	..			
0 mg/ml	0·05	..		
8 mg/ml	<0·0001	0·04	..	
36 mg/ml	0·002	0·32	0·27	..
Week 4				
CS	..			
0 mg/ml	0·22	..		
8 mg/ml	0·0009	0·05	..	
36 mg/ml	0·0004	0·04	0·94	..
Week 8				
CS	..			
0 mg/ml	0·17	..		
8 mg/ml	0·003	0·13	..	
36 mg/ml	0·001	0·09	0·86	..
Week 12				
CS	..			
0 mg/ml	0·33	..		

8 mg/ml	0·04	0·004	··	
36 mg/ml	0·02	0·001	0·87	··
Week 16				
CS	··			
0 mg/ml	0·73	··		
8 mg/ml	0·0002	0·002	··	
36 mg/ml	<0·0001	0·0008	0·94	··
Week 20				
CS	··			
0 mg/ml	0·87	··		
8 mg/ml	0·01	0·01	··	
36 mg/ml	<0·0001	<0·0001	0·12	··
Week 24				
CS	··			
0 mg/ml	0·55	··		
8 mg/ml	0·23	0·59	··	
36 mg/ml	0·01[S]	0·05	0·16	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

***** Bonferroni correction alpha=0.008, between all conditions.

S Significant difference between cigarette substitute and 36 mg/ml at week 2 for unadjusted model with p=0·007; significant difference between cigarette substitute and 8 mg/ml at week 4 for unadjusted model with p=0·005; significant difference between 0 mg/ml and 36 mg/ml at week 4 for unadjusted model with p=0·005; significant difference between 0 mg/ml and 36 mg/ml at week 12 for unadjusted model with p=0·005; significant difference between 0 mg/ml and 36 mg/ml at week 16 for unadjusted model with p=0·007; significant difference between cigarette substitute and 8 mg/ml at week 20 for unadjusted model with p=0·006; significant difference between cigarette substitute and 36 mg/ml at week 24 for unadjusted model with p=0·005. All compared to Bonferroni correction alpha=0·05/6=0·00833.

Table S43. P-values for pairwise comparisons between conditions at each time point for exhaled carbon monoxide using per-protocol method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·15	..		
8 mg/ml	0·30	0·69	..	
36 mg/ml	0·26	0·72	0·96	..
Week 1				
CS	..			
0 mg/ml	0·18	..		
8 mg/ml	0·0007	0·05	..	
36 mg/ml	0·07	0·71	0·10	..
Week 2				
CS	..			
0 mg/ml	0·15	..		
8 mg/ml	0·0003	0·04	..	
36 mg/ml	0·009	0·30	0·27	..
Week 4				
CS	..			
0 mg/ml	0·42	..		
8 mg/ml	0·002	0·03	..	
36 mg/ml	0·003	0·04	0·84	..
Week 8				
CS	..			
0 mg/ml	0·10	..		
8 mg/ml	0·002	0·15	..	
36 mg/ml	0·0008	0·12	0·92	..
Week 12				
CS	..			
0 mg/ml	0·67	..		
8 mg/ml	0·04	0·02	..	
36 mg/ml	0·01	0·004	0·66	..
Week 16				
CS	..			
0 mg/ml	0·71	..		
8 mg/ml	0·001	0·01[S]	..	
36 mg/ml	0·0002	0·002	0·75	..
Week 20				
CS	..			
0 mg/ml	0·66	..		
8 mg/ml	0·01[S]	0·03	..	
36 mg/ml	<0·0001	0·0004	0·17	..
Week 24				
CS	..			
0 mg/ml	0·41	..		
8 mg/ml	0·07	0·36	..	
36 mg/ml	0·003	0·05	0·29	..
Adjusted Model*				
Week 0				

	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·26	..		
8 mg/ml	0·68	0·52	..	
36 mg/ml	0·76	0·41	0·90	..
Week 1				
CS	..			
0 mg/ml	0·13	..		
8 mg/ml	0·002	0·12	..	
36 mg/ml	0·29	0·61	0·03	..
Week 2				
CS	..			
0 mg/ml	0·07	..		
8 mg/ml	0·0002	0·06	..	
36 mg/ml	0·02	0·72	0·11	..
Week 4				
CS	..			
0 mg/ml	0·40	..		
8 mg/ml	0·001	0·02	..	
36 mg/ml	0·005	0·07	0·54	..
Week 8				
CS	..			
0 mg/ml	0·17	..		
8 mg/ml	0·01	0·25	..	
36 mg/ml	0·002	0·13	0·79	..
Week 12				
CS	..			
0 mg/ml	0·37	..		
8 mg/ml	0·08	0·02	..	
36 mg/ml	0·01	0·001	0·56	..
Week 16				
CS	..			
0 mg/ml	0·68	..		
8 mg/ml	0·0006	0·01[S]	..	
36 mg/ml	<0·0001	0·0006	0·70	..
Week 20				
CS	..			
0 mg/ml	0·88	..		
8 mg/ml	0·03	0·05	..	
36 mg/ml	<0·0001	<0·0001	0·06	..
Week 24				
CS	..			
0 mg/ml	0·34	..		
8 mg/ml	0·21	0·77	..	
36 mg/ml	0·002	0·06	0·12	..

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

S Bonferroni correction alpha=0.008, between all conditions.

S Significant difference between 0 mg/ml and 8 mg/ml at week 16 for unadjusted model with p=0·007; significant difference between cigarette substitute and 8 mg/ml at week 20 for unadjusted model with p=0·007; significant difference between 0 mg/ml and 8 mg/ml at week 16 for adjusted model with p=0·005. All compared to Bonferroni correction alpha=0·05/6=0·00833.

Table S44. P-values for pairwise comparisons between conditions at each time point for exhaled carbon monoxide using baseline-carried-forward method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·84	..		
8 mg/ml	0·20	0·29	..	
36 mg/ml	0·23	0·32	0·94	..
Week 1				
CS	..			
0 mg/ml	0·72	..		
8 mg/ml	0·0007	0·002	..	
36 mg/ml	0·01	0·03	0·38	..
Week 2				
CS	..			
0 mg/ml	0·53	..		
8 mg/ml	0·0003	0·003	..	
36 mg/ml	0·004	0·03	0·44	..
Week 4				
CS	..			
0 mg/ml	0·85	..		
8 mg/ml	0·003	0·002	..	
36 mg/ml	0·0004	0·0002	0·54	..
Week 8				
CS	..			
0 mg/ml	0·78	..		
8 mg/ml	0·01[S]	0·01	..	
36 mg/ml	0·002	0·01[S]	0·79	..
Week 12				
CS	..			
0 mg/ml	0·17	..		
8 mg/ml	0·04	0·0006	..	
36 mg/ml	0·02	0·0001	0·71	..

Week 16				
CS	..			
0 mg/ml	0·74	..		
8 mg/ml	0·0004	0·0001	..	
36 mg/ml	0·001	0·0003	0·80	..
Week 20				
CS	..			
0 mg/ml	0·55	..		
8 mg/ml	0·01[S]	0·001	..	
36 mg/ml	0·0002	<0·0001	0·32	..
Week 24				
CS	..			
0 mg/ml	0·45	..		
8 mg/ml	0·11	0·02	..	
36 mg/ml	0·02	0·002	0·47	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·55	..		
8 mg/ml	0·56	0·98	..	
36 mg/ml	0·53	0·99	0·97	..
Week 1				
CS	..			
0 mg/ml	0·21	..		
8 mg/ml	0·0009	0·05	..	
36 mg/ml	0·02	0·29	0·32	..
Week 2				
CS	..			
0 mg/ml	0·08	..		
8 mg/ml	<0·0001	0·02	..	
36 mg/ml	0·001	0·16	0·29	..
Week 4				
CS	..			

0 mg/ml	0·43	··		
8 mg/ml	0·0005	0·01[S]	··	
36 mg/ml	<0·0001	0·001	0·61	··
Week 8				
CS	··			
0 mg/ml	0·46	··		
8 mg/ml	0·01	0·08	··	
36 mg/ml	0·0008	0·01	0·46	··
Week 12				
CS	··			
0 mg/ml	0·15	··		
8 mg/ml	0·05	0·0009	··	
36 mg/ml	0·01	<0·0001	0·55	··
Week 16				
CS	··			
0 mg/ml	0·75	··		
8 mg/ml	0·0003	0·001	··	
36 mg/ml	<0·0001	0·0002	0·71	··
Week 20				
CS	··			
0 mg/ml	0·62	··		
8 mg/ml	0·02	0·004	··	
36 mg/ml	<0·0001	<0·0001	0·06	··
Week 24				
CS	··			
0 mg/ml	0·86	··		
8 mg/ml	0·32	0·26	··	
36 mg/ml	0·01	0·01[S]	0·12	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0.008, between all conditions.

S Significant difference between cigarette substitute and 8 mg/ml at week 8 for unadjusted model with p=0·005; significant difference between 0 mg/ml and 36 mg/ml at week 8 for unadjusted model with p=0·005; significant difference between cigarette substitute and 8 mg/ml at week 20 for unadjusted model with p=0·007; significant difference between 0 mg/ml and 8 mg/ml at week 4 for adjusted model with p=0·0081; significant difference between 0 mg/ml and 36 mg/ml at week 24 for adjusted model with p=0·007, comparing to Bonferroni correction alpha=0·05/6=0·0083.

Table S45. P-values for pairwise comparisons between conditions at each time point for exhaled carbon monoxide using last-observation-carried-forward method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·83	..		
8 mg/ml	0·19	0·28	..	
36 mg/ml	0·22	0·31	0·94	..
Week 1				
CS	..			
0 mg/ml	0·71	..		
8 mg/ml	0·0005	0·002	..	
36 mg/ml	0·01	0·03	0·36	..
Week 2				
CS	..			
0 mg/ml	0·46	..		
8 mg/ml	0·0002	0·002	..	
36 mg/ml	0·01[S]	0·04	0·34	..
Week 4				
CS	..			
0 mg/ml	0·95	..		
8 mg/ml	0·003	0·003	..	
36 mg/ml	0·001	0·001	0·76	..
Week 8				
CS	..			
0 mg/ml	0·71	..		
8 mg/ml	0·001	0·004	..	
36 mg/ml	0·0007	0·003	0·88	..
Week 12				
CS	..			
0 mg/ml	0·25	..		
8 mg/ml	0·03	0·0008	..	
36 mg/ml	0·02	0·0004	0·83	..
Week 16				
CS	..			
0 mg/ml	0·47	..		
8 mg/ml	0·001	<0·0001	..	
36 mg/ml	0·003	0·0003	0·73	..
Week 20				
CS	..			
0 mg/ml	0·41	..		
8 mg/ml	0·003	0·0002	..	
36 mg/ml	0·002	<0·0001	0·83	..
Week 24				
CS	..			
0 mg/ml	0·42	..		
8 mg/ml	0·04	0·01[S]	..	
36 mg/ml	0·05	0·01[S]	0·95	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**

CS	..			
0 mg/ml	0·55	..		
8 mg/ml	0·53	0·97	..	
36 mg/ml	0·42	0·84	0·87	..
Week 1				
CS	..			
0 mg/ml	0·22	..		
8 mg/ml	0·001	0·05	..	
36 mg/ml	0·01	0·23	0·42	..
Week 2				
CS	..			
0 mg/ml	0·06	..		
8 mg/ml	<0·0001	0·03	..	
36 mg/ml	0·002	0·26	0·25	..
Week 4				
CS	..			
0 mg/ml	0·36	..		
8 mg/ml	0·0007	0·02	..	
36 mg/ml	0·0005	0·01	0·98	..
Week 8				
CS	..			
0 mg/ml	0·31	..		
8 mg/ml	0·001	0·03	..	
36 mg/ml	0·0003	0·01	0·71	..
Week 12				
CS	..			
0 mg/ml	0·41	..		
8 mg/ml	0·02	0·002	..	
36 mg/ml	0·01	0·001	0·90	..
Week 16				
CS	..			
0 mg/ml	0·87	..		
8 mg/ml	0·0003	0·0008	..	
36 mg/ml	0·0001	0·0004	0·88	..
Week 20				
CS	..			
0 mg/ml	0·81	..		
8 mg/ml	0·01[S]	0·004	..	
36 mg/ml	0·0002	<0·0001	0·33	..
Week 24				
CS	..			
0 mg/ml	0·93	..		
8 mg/ml	0·09	0·11	..	
36 mg/ml	0·02	0·03	0·53	..

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

***** Bonferroni correction alpha=0·008, between all conditions.

S Significant difference between cigarette substitute and 36 mg/ml at week 2 for unadjusted model with p=0·005; significant difference between 0 mg/ml and 8 mg/ml at week 24 for unadjusted model with p=0·005; significant difference between 0 mg/ml and 36 mg/ml at week 24 for unadjusted model with p=0·006; significant difference between cigarette substitute and 8 mg/ml at week 20 for adjusted model with p=0·007, comparing to Bonferroni correction alpha=0·05/6=0·0083.

Table S46. P-values for pairwise comparisons relative to baseline within each condition for exhaled carbon monoxide using multiple imputation method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·01	0·02	<0·0001	<0·0001
Week 2	0·03	0·01[S]	<0·0001	<0·0001
Week 4	0·01	0·01	<0·0001	<0·0001
Week 8	0·04	0·02	<0·0001	<0·001
Week 12	0·01	0·16	0·0001	0·0001
Week 16	0·18	0·30	0·0002	0·0009
Week 20	0·03	0·12	0·0009	<0·0001
Week 24	0·05	0·15	0·01	0·002
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·01	0·01	<0·0001	<0·0001
Week 2	0·02	0·003	<0·0001	<0·0001
Week 4	0·004	0·002	<0·0001	<0·0001
Week 8	0·02	0·01	<0·0001	<0·0001
Week 12	0·004	0·10	<0·0001	<0·0001
Week 16	0·09	0·21	<0·0001	<0·0001
Week 20	0·01	0·06	0·0002	<0·0001
Week 24	0·02	0·07	0·003	0·001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

[S] Significant difference between week 0 and week 2 in 0 mg/ml for unadjusted model with p=0·00623, comparing to Bonferroni correction alpha=0·05/8=0·00625.

Table S47. P-values for pairwise comparisons relative to baseline within each condition for exhaled carbon monoxide using intent-to-treat method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·004	0·003	<0·0001	<0·0001
Week 2	0·02	0·004	<0·0001	<0·0001
Week 4	0·002	0·004	<0·0001	<0·0001
Week 8	0·05	0·004	<0·0001	<0·0001
Week 12	0·01[S]	0·11	0·0003	<0·0001
Week 16	0·19	0·26	0·0002	0·0008
Week 20	0·06	0·09	0·0002	<0·0001
Week 24	0·03	0·02	0·01[S]	0·0004
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·002	0·0002	<0·0001	<0·0001
Week 2	0·02	0·0003	<0·0001	<0·0001
Week 4	0·003	0·0007	<0·0001	<0·0001
Week 8	0·02	0·003	<0·0001	<0·0001
Week 12	0·003	0·28	<0·0001	<0·0001
Week 16	0·32	0·47	<0·0001	<0·0001
Week 20	0·02	0·19	<0·0001	<0·0001
Week 24	0·01	0·02	0·002	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0.006, relative to baseline (week 0).

S Significant difference between week 0 and week 12 in cigarette substitute condition for unadjusted model with p=0·0057; significant difference between week 0 and week 24 in 8 mg/ml condition for unadjusted model with p=0·0057,comparing to Bonferroni correction alpha=0·05/8=0·0063.

Table S48. P-values for pairwise comparisons relative to baseline within each condition for exhaled carbon monoxide using per-protocol method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·04	0·10	<0·0001	0·002
Week 2	0·15	0·19	<0·0001	0·0009
Week 4	0·01	0·15	<0·0001	<0·0001
Week 8	0·12	0·11	0·0003	<0·0001
Week 12	0·01	0·78	0·001	<0·0001
Week 16	0·20	0·93	0·0009	<0·0001
Week 20	0·12	0·68	0·002	<0·0001
Week 24	0·08	0·34	0·02	0·0004
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·03	0·02	<0·0001	0·002
Week 2	0·14	0·05	<0·0001	0·0002
Week 4	0·02	0·07	<0·0001	<0·0001
Week 8	0·08	0·07	0·0003	<0·0001
Week 12	0·01	0·81	0·0008	<0·0001
Week 16	0·36	0·90	0·0003	<0·0001
Week 20	0·08	0·55	0·001	<0·0001
Week 24	0·06	0·15	0·02	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

Table S49. P-values for pairwise comparisons relative to baseline within each condition for exhaled CO using baseline-carried-forward method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·004	0·001	<0·0001	<0·0001
Week 2	0·04	0·01	<0·0001	<0·0001
Week 4	0·02	0·06	<0·0001	<0·0001
Week 8	0·08	0·07	0·0003	<0·0001
Week 12	0·04	0·78	0·003	0·0006
Week 16	0·66	0·88	0·004	0·01
Week 20	0·28	0·81	0·01	0·0002
Week 24	0·10	0·51	0·05	0·01[S]
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·002	0·0001	<0·0001	<0·0001
Week 2	0·03	0·0007	<0·0001	<0·0001
Week 4	0·01	0·01	<0·0001	<0·0001
Week 8	0·04	0·03	<0·0001	<0·0001
Week 12	0·02	0·90	0·0004	<0·0001
Week 16	0·75	0·98	0·0009	0·0001
Week 20	0·17	0·82	0·002	<0·0001
Week 24	0·04	0·23	0·02	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

S Significant difference between week 0 and week 24 in 36 mg/ml condition for unadjusted model with p=0·005, comparing to Bonferroni correction alpha=0·05/8=0·0063.

Table S50. P-values for pairwise comparisons relative to baseline within each condition for exhaled carbon monoxide using last-observation-carried-forward method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·002	0·0007	<0·0001	<0·0001
Week 2	0·01	0·0009	<0·0001	<0·0001
Week 4	0·002	0·01[S]	<0·0001	<0·0001
Week 8	0·02	0·01	<0·0001	<0·0001
Week 12	0·003	0·14	<0·0001	<0·0001
Week 16	0·06	0·40	<0·0001	0·0002
Week 20	0·03	0·27	<0·0001	<0·0001
Week 24	0·01	0·14	0·001	0·001
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	0·001	<0·0001	<0·0001	<0·0001
Week 2	0·01	<0·0001	<0·0001	<0·0001
Week 4	0·001	0·0005	<0·0001	<0·0001
Week 8	0·01	0·003	<0·0001	<0·0001
Week 12	0·001	0·08	<0·0001	<0·0001
Week 16	0·07	0·19	<0·0001	<0·0001
Week 20	0·01	0·08	<0·0001	<0·0001
Week 24	0·002	0·02	<0·0001	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, week 0 urinary total NNAL (pg/mg creatinine-transformed), week 0 body mass index, education level, total household income, age of smoking initiation, week 0 waist circumference, week 0 partial INTERHEART non-laboratory score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0.006, relative to baseline (week 0).

S Significant difference between week 0 and week 4 in 0 mg/ml condition for unadjusted model with p=0·005; comparing to Bonferroni correction alpha=0·05/8=0·0063.

Table S51. Estimated mean cigarettes smoked per day in unadjusted and adjusted mixed models using multiple imputation method

CPD	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)
Week 0	130	18·37 (17·15, 19·59)	130	18·79 (17·57, 20·01)	130	19·45 (18·23, 20·67)	130	17·76 (16·54, 18·98)
Week 1	130	15·37 (14·13, 16·60)	130	13·39 (12·13, 14·66)	130	13·11 (11·88, 14·34)	130	12·02 (10·78, 13·26)
Week 2	130	14·58 (13·26, 15·90)	130	12·15 (10·89, 13·4)	130	12·35 (11·07, 13·64)	130	10·87 (9·60, 12·14)
Week 4	130	13·26 (12·03, 14·50)	130	10·53 (9·24, 11·82)	130	10·41 (9·11, 11·71)	130	9·38 (8·13, 10·63)
Week 8	130	12·77 (11·37, 14·17)	130	10·16 (8·84, 11·48)	130	10·47 (9·22, 11·73)	130	9·02 (7·66, 10·39)
Week 12	130	12·03 (10·74, 13·32)	130	9·95 (8·65, 11·24)	130	9·75 (8·15, 11·36)	130	8·10 (6·77, 9·42)
Week 16	130	11·77 (10·46, 13·08)	130	9·26 (7·92, 10·60)	130	9·69 (8·38, 11·00)	130	7·38 (5·93, 8·83)
Week 20	130	11·30 (10·05, 12·54)	130	9·35 (7·71, 10·99)	130	9·27 (7·99, 10·54)	130	7·30 (5·99, 8·60)
Week 24	130	11·23 (9·76, 12·71)	130	9·21 (7·89, 10·53)	130	9·12 (7·61, 10·64)	130	7·43 (6·14, 8·71)
	Adjusted Model							
Week 0	130	17·90 (16·98, 18·82)	130	17·93 (16·99, 18·86)	130	18·49 (17·56, 19·42)	130	17·66 (16·73, 18·59)
Week 1	130	14·90 (13·97, 15·82)	130	12·53 (11·56, 13·51)	130	12·15 (11·21, 13·10)	130	11·92 (10·95, 12·89)
Week 2	130	14·11 (13·06, 15·15)	130	11·29 (10·32, 12·25)	130	11·39 (10·41, 12·38)	130	10·77 (9·77, 11·77)
Week 4	130	12·79 (11·85, 13·74)	130	9·67 (8·64, 10·71)	130	9·45 (8·48, 10·42)	130	9·28 (8·32, 10·24)
Week 8	130	12·30 (11·11, 13·48)	130	9·30 (8·22, 10·37)	130	9·51 (8·56, 10·47)	130	8·93 (7·77, 10·08)
Week 12	130	11·56 (10·59, 12·53)	130	9·09 (8·06, 10·12)	130	8·79 (7·37, 10·22)	130	8·00 (6·99, 9·01)
Week 16	130	11·30 (10·25, 12·35)	130	8·40 (7·29, 9·50)	130	8·73 (7·67, 9·80)	130	7·28 (6·05, 8·52)
Week 20	130	10·83 (9·88, 11·78)	130	8·49 (7·02, 9·96)	130	8·31 (7·32, 9·29)	130	7·20 (6·18, 8·22)
Week 24	130	10·77 (9·53, 12·00)	130	8·35 (7·28, 9·42)	130	8·16 (6·79, 9·53)	130	7·33 (6·31, 8·35)

Note: CPD, cigarettes smoked per day; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S52. Estimated mean cigarettes smoked per day in unadjusted and adjusted mixed models using intent-to-treat method

CPD	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)
Week 0	130	18·37 (17·13, 19·61)	130	18·79 (17·55, 20·02)	130	19·45 (18·21, 20·69)	130	17·76 (16·52, 18·99)
Week 1	120	15·42 (14·17, 16·67)	112	13·54 (12·28, 14·80)	116	13·19 (11·94, 14·44)	120	12·20 (10·95, 13·45)
Week 2	115	14·56 (13·30, 15·82)	104	12·27 (10·98, 13·55)	116	12·03 (10·77, 13·29)	113	10·84 (9·58, 12·11)
Week 4	115	13·23 (11·96, 14·50)	95	10·22 (8·89, 11·54)	110	10·13 (8·85, 11·41)	112	9·25 (7·97, 10·52)
Week 8	95	12·67 (11·36, 13·99)	84	9·70 (8·32, 11·08)	92	9·59 (8·26, 10·92)	95	8·63 (7·31, 9·95)
Week 12	92	11·82 (10·47, 13·17)	78	9·70 (8·26, 11·13)	84	9·04 (7·66, 10·41)	93	7·76 (6·41, 9·11)
Week 16	86	11·68 (10·29, 13·07)	71	8·83 (7·33, 10·32)	78	9·31 (7·89, 10·74)	84	6·98 (5·58, 8·38)
Week 20	86	11·62 (10·21, 13·04)	65	9·50 (7·95, 11·06)	72	8·52 (7·04, 10·00)	78	6·76 (5·31, 8·21)
Week 24	91	11·31 (9·88, 12·74)	69	8·62 (7·04, 10·21)	74	8·02 (6·50, 9·54)	80	6·62 (5·13, 8·10)
	Adjusted Model							
Week 0	130	17·61 (16·61, 18·61)	130	17·68 (16·65, 18·7)	130	18·15 (17·1, 19·19)	130	17·43 (16·42, 18·44)
Week 1	120	14·76 (13·75, 15·77)	112	12·50 (11·45, 13·55)	116	11·92 (10·86, 12·98)	120	11·91 (10·89, 12·94)
Week 2	115	13·94 (12·91, 14·96)	104	11·40 (10·32, 12·48)	116	10·91 (9·84, 11·98)	113	10·57 (9·53, 11·61)
Week 4	115	12·66 (11·63, 13·7)	95	9·40 (8·29, 10·51)	110	9·01 (7·93, 10·10)	112	8·91 (7·86, 9·96)
Week 8	95	12·09 (11·02, 13·17)	84	8·63 (7·47, 9·79)	92	8·74 (7·60, 9·88)	95	8·31 (7·21, 9·40)
Week 12	92	11·03 (9·93, 12·13)	78	8·70 (7·50, 9·91)	84	7·88 (6·69, 9·06)	93	7·44 (6·32, 8·56)
Week 16	86	10·89 (9·76, 12·02)	71	7·81 (6·57, 9·06)	78	8·39 (7·16, 9·62)	84	6·70 (5·54, 7·87)
Week 20	86	10·80 (9·66, 11·95)	65	8·50 (7·21, 9·80)	72	7·58 (6·31, 8·85)	78	6·47 (5·27, 7·68)
Week 24	91	10·44 (9·30, 11·58)	69	7·73 (6·43, 9·03)	74	7·14 (5·84, 8·43)	80	6·31 (5·09, 7·53)

Note: CPD, cigarettes smoked per day; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S53. Estimated mean cigarettes smoked per day in unadjusted and adjusted mixed models using per-protocol method

CPD	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)
Week 0	86	18·57 (17·05, 20·09)	67	18·31 (16·59, 20·03)	67	18·51 (16·79, 20·23)	79	17·37 (15·78, 18·95)
Week 1	83	15·78 (14·26, 17·31)	65	12·91 (11·18, 14·63)	64	12·75 (11·02, 14·48)	78	12·66 (11·07, 14·24)
Week 2	84	15·08 (13·56, 16·60)	66	11·67 (9·95, 13·40)	67	11·63 (9·91, 13·35)	78	11·00 (9·41, 12·58)
Week 4	86	13·69 (12·17, 15·21)	67	9·78 (8·06, 11·50)	67	9·41 (7·69, 11·13)	79	9·25 (7·66, 10·83)
Week 8	80	12·98 (11·46, 14·51)	66	9·33 (7·61, 11·06)	66	9·01 (7·29, 10·73)	75	8·45 (6·86, 10·04)
Week 12	86	11·98 (10·46, 13·50)	67	9·20 (7·48, 10·92)	67	8·69 (6·97, 10·41)	79	7·43 (5·85, 9·02)
Week 16	81	11·91 (10·39, 13·44)	64	8·28 (6·55, 10·01)	64	9·01 (7·28, 10·74)	77	6·67 (5·08, 8·26)
Week 20	81	12·02 (10·49, 13·54)	61	9·10 (7·37, 10·83)	65	8·40 (6·67, 10·12)	77	6·52 (4·93, 8·11)
Week 24	86	11·40 (9·88, 12·92)	67	8·26 (6·53, 9·98)	67	7·80 (6·07, 9·52)	79	6·35 (4·76, 7·93)
	Adjusted Model							
Week 0	86	17·24 (15·94, 18·54)	67	17·09 (15·61, 18·56)	67	17·53 (16·02, 19·03)	79	16·73 (15·33, 18·13)
Week 1	83	14·37 (13·07, 15·68)	65	11·88 (10·40, 13·36)	64	11·81 (10·3, 13·32)	78	12·08 (10·68, 13·48)
Week 2	84	13·65 (12·34, 14·95)	66	10·77 (9·29, 12·25)	67	10·79 (9·28, 12·29)	78	10·42 (9·01, 11·82)
Week 4	86	12·26 (10·96, 13·56)	67	8·92 (7·44, 10·40)	67	8·34 (6·83, 9·84)	79	8·56 (7·16, 9·96)
Week 8	80	11·55 (10·24, 12·87)	66	8·17 (6·69, 9·65)	66	8·11 (6·60, 9·61)	75	7·84 (6·43, 9·24)
Week 12	86	10·37 (9·06, 11·67)	67	8·05 (6·57, 9·52)	67	7·51 (6·01, 9·02)	79	6·76 (5·36, 8·16)
Week 16	81	10·37 (9·06, 11·68)	64	7·06 (5·58, 8·55)	64	8·03 (6·52, 9·54)	77	6·00 (4·60, 7·40)
Week 20	81	10·51 (9·20, 11·82)	61	7·78 (6·29, 9·27)	65	7·32 (5·81, 8·83)	77	5·85 (4·45, 7·25)
Week 24	86	9·87 (8·56, 11·17)	67	7·09 (5·61, 8·57)	67	6·66 (5·15, 8·16)	79	5·66 (4·26, 7·06)

Note: CPD, cigarettes smoked per day; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second. Sample size included participants who have available cigarettes smoked per day at week 0, 4, 12 and 24, which is N=86, 67, 67 and 79 for CS, 0 mg/ml, 8 mg/ml and 36 mg/ml, respectively.

Table S54. Estimated mean cigarettes smoked per day in unadjusted and adjusted mixed models using baseline-carried forward method

CPD	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)
Week 0	130	18·37 (16·89, 19·85)	130	18·79 (17·30, 20·27)	130	19·45 (17·97, 20·93)	130	17·76 (16·28, 19·24)
Week 1	130	15·68 (14·2, 17·16)	130	14·28 (12·80, 15·77)	130	13·83 (12·35, 15·31)	130	12·61 (11·13, 14·09)
Week 2	130	15·23 (13·75, 16·71)	130	13·62 (12·14, 15·10)	130	13·25 (11·77, 14·73)	130	11·78 (10·30, 13·26)
Week 4	130	13·96 (12·48, 15·45)	130	12·66 (11·18, 14·15)	130	11·87 (10·39, 13·35)	130	10·56 (9·08, 12·04)
Week 8	130	14·48 (13·00, 15·96)	130	12·88 (11·39, 14·36)	130	13·01 (11·53, 14·49)	130	11·13 (9·65, 12·61)
Week 12	130	13·88 (12·40, 15·36)	130	13·33 (11·85, 14·81)	130	12·92 (11·44, 14·41)	130	10·77 (9·29, 12·25)
Week 16	130	13·86 (12·38, 15·35)	130	13·34 (11·86, 14·82)	130	13·42 (11·94, 14·90)	130	11·02 (9·54, 12·50)
Week 20	130	13·72 (12·24, 15·20)	130	14·06 (12·58, 15·55)	130	13·67 (12·19, 15·16)	130	11·24 (9·76, 12·72)
Week 24	130	13·41 (11·92, 14·89)	130	13·47 (11·99, 14·95)	130	13·48 (11·99, 14·96)	130	11·05 (9·57, 12·53)
	Adjusted Model							
Week 0	130	18·05 (16·93, 19·18)	130	17·97 (16·82, 19·13)	130	18·36 (17·19, 19·53)	130	18·03 (16·89, 19·17)
Week 1	130	15·46 (14·33, 16·58)	130	13·50 (12·34, 14·65)	130	12·75 (11·58, 13·92)	130	12·93 (11·79, 14·06)
Week 2	130	15·05 (13·92, 16·17)	130	13·01 (11·85, 14·16)	130	12·20 (11·03, 13·37)	130	12·03 (10·89, 13·16)
Week 4	130	13·83 (12·71, 14·96)	130	11·86 (10·71, 13·02)	130	10·93 (9·76, 12·10)	130	10·71 (9·58, 11·85)
Week 8	130	14·3 (13·17, 15·42)	130	11·91 (10·76, 13·07)	130	12·08 (10·91, 13·25)	130	11·39 (10·25, 12·53)
Week 12	130	13·38 (12·25, 14·5)	130	12·37 (11·22, 13·53)	130	11·82 (10·65, 12·99)	130	11·01 (9·87, 12·15)
Week 16	130	13·44 (12·32, 14·57)	130	12·35 (11·2, 13·51)	130	12·52 (11·35, 13·69)	130	11·29 (10·15, 12·42)
Week 20	130	13·28 (12·16, 14·40)	130	13·13 (11·98, 14·29)	130	12·70 (11·53, 13·87)	130	11·41 (10·27, 12·54)
Week 24	130	12·95 (11·82, 14·07)	130	12·55 (11·40, 13·71)	130	12·51 (11·34, 13·68)	130	11·20 (10·06, 12·34)

Note: CPD, cigarettes smoked per day; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S55. Estimated mean cigarettes smoked per day in unadjusted and adjusted mixed models using last-observation-carried-forward method

CPD	Unadjusted Model							
Condition	CS		0 mg/ml		8 mg/ml		36 mg/ml	
Week	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)	N	Estimated Mean (95% CI)
Week 0	130	18·37 (17·04, 19·7)	130	18·79 (17·46, 20·12)	130	19·45 (18·12, 20·78)	130	17·76 (16·43, 19·09)
Week 1	130	15·68 (14·35, 17·01)	130	14·28 (12·95, 15·61)	130	13·83 (12·50, 15·16)	130	12·61 (11·28, 13·94)
Week 2	130	14·80 (13·47, 16·13)	130	13·11 (11·78, 14·44)	130	12·56 (11·23, 13·88)	130	11·31 (9·98, 12·64)
Week 4	130	13·67 (12·34, 15·00)	130	11·59 (10·26, 12·92)	130	10·94 (9·61, 12·26)	130	9·87 (8·54, 11·20)
Week 8	130	13·20 (11·87, 14·53)	130	11·23 (9·90, 12·56)	130	10·48 (9·16, 11·81)	130	9·49 (8·16, 10·82)
Week 12	130	12·54 (11·21, 13·87)	130	11·26 (9·93, 12·59)	130	10·15 (8·82, 11·48)	130	8·84 (7·51, 10·17)
Week 16	130	12·35 (11·02, 13·68)	130	10·80 (9·47, 12·13)	130	10·35 (9·02, 11·68)	130	8·34 (7·01, 9·67)
Week 20	130	12·29 (10·96, 13·62)	130	11·23 (9·90, 12·56)	130	9·89 (8·56, 11·22)	130	8·26 (6·93, 9·59)
Week 24	130	12·05 (10·72, 13·38)	130	10·87 (9·54, 12·19)	130	9·66 (8·33, 10·99)	130	8·20 (6·87, 9·53)
	Adjusted Model							
Week 0	130	17·93 (16·83, 19·04)	130	17·98 (16·84, 19·11)	130	18·45 (17·30, 19·61)	130	17·78 (16·66, 18·91)
Week 1	130	15·34 (14·23, 16·44)	130	13·50 (12·36, 14·64)	130	12·84 (11·69, 13·99)	130	12·68 (11·56, 13·80)
Week 2	130	14·48 (13·37, 15·58)	130	12·45 (11·31, 13·59)	130	11·64 (10·48, 12·79)	130	11·38 (10·25, 12·50)
Week 4	130	13·41 (12·3, 14·51)	130	10·91 (9·77, 12·04)	130	9·98 (8·82, 11·13)	130	9·83 (8·71, 10·95)
Week 8	130	12·94 (11·83, 14·05)	130	10·38 (9·24, 11·51)	130	9·62 (8·46, 10·77)	130	9·49 (8·37, 10·61)
Week 12	130	12·16 (11·06, 13·27)	130	10·44 (9·31, 11·58)	130	9·08 (7·93, 10·23)	130	8·82 (7·70, 9·94)
Week 16	130	11·96 (10·86, 13·07)	130	9·94 (8·81, 11·08)	130	9·40 (8·24, 10·55)	130	8·32 (7·20, 9·44)
Week 20	130	11·98 (10·87, 13·08)	130	10·35 (9·21, 11·49)	130	8·93 (7·78, 10·09)	130	8·24 (7·11, 9·36)
Week 24	130	11·72 (10·62, 12·83)	130	10·02 (8·88, 11·15)	130	8·65 (7·50, 9·80)	130	8·16 (7·04, 9·29)

Note: CPD, cigarettes smoked per day; CS, cigarette substitute; CI, confidence interval. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

Table S56. P-values for pairwise comparisons between conditions at each time point for cigarettes smoked per day using multiple imputation method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·64	..		
8 mg/ml	0·22	0·45	..	
36 mg/ml	0·49	0·24	0·05	..
Week 1				
CS	..			
0 mg/ml	0·03	..		
8 mg/ml	0·01	0·75	..	
36 mg/ml	0·0002	0·12	0·22	..
Week 2				
CS	..			
0 mg/ml	0·01	..		
8 mg/ml	0·01	0·82	..	
36 mg/ml	<0·0001	0·16	0·10	..
Week 4				
CS	..			
0 mg/ml	0·003	..		
8 mg/ml	0·002	0·90	..	
36 mg/ml	<0·0001	0·21	0·26	..
Week 8				
CS	..			
0 mg/ml	0·01[S]	..		
8 mg/ml	0·02	0·73	..	
36 mg/ml	<0·0001	0·23	0·14	..
Week 12				
CS	..			
0 mg/ml	0·03	..		
8 mg/ml	0·05	0·86	..	
36 mg/ml	<0·0001	0·06	0·11	..
Week 16				
CS	..			
0 mg/ml	0·01[S]	..		
8 mg/ml	0·03	0·64	..	
36 mg/ml	<0·0001	0·04	0·02	..
Week 20				

CS	··			
0 mg/ml	0·06	··		
8 mg/ml	0·02	0·93	··	
36 mg/ml	<0·0001	0·07	0·033	··
Week 24				
CS	··			
0 mg/ml	0·04	··		
8 mg/ml	0·03	0·93	··	
36 mg/ml	0·0002	0·05	0·10	··
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	··			
0 mg/ml	0·96	··		
8 mg/ml	0·34	0·36	··	
36 mg/ml	0·70	0·67	0·18	··
Week 1				
CS	··			
0 mg/ml	0·0005	··		
8 mg/ml	<0·0001	0·55	··	
36 mg/ml	<0·0001	0·33	0·71	··
Week 2				
CS	··			
0 mg/ml	<0·0001	··		
8 mg/ml	<0·0001	0·87	··	
36 mg/ml	<0·0001	0·44	0·33	··
Week 4				
CS	··			
0 mg/ml	<0·0001	··		
8 mg/ml	<0·0001	0·76	··	
36 mg/ml	<0·0001	0·57	0·80	··
Week 8				
CS	··			
0 mg/ml	<0·0001	··		
8 mg/ml	0·0008	0·75	··	
36 mg/ml	<0·0001	0·60	0·43	··
Week 12				
CS	··			
0 mg/ml	0·0005	··		

8 mg/ml	0·01	0·75	··	
36 mg/ml	<0·0001	0·15	0·33	··
Week 16				
CS	··			
0 mg/ml	<0·0001	··		
8 mg/ml	0·0005	0·62	··	
36 mg/ml	<0·0001	0·09	0·05	··
Week 20				
CS	··			
0 mg/ml	0·01[S]	··		
8 mg/ml	<0·0001	0·81	··	
36 mg/ml	<0·0001	0·17	0·10	··
Week 24				
CS	··			
0 mg/ml	0·002	··		
8 mg/ml	0·001	0·80	··	
36 mg/ml	<0·0001	0·12	0·31	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·008, between all conditions.

S Significant difference between cigarette substitute and 0 mg/ml at week 8 in unadjusted model with p=0·005; significant difference between cigarette substitute and 0 mg/ml at week 16 in unadjusted model with p-value=0·0077; significant difference between cigarette substitute and 0 mg/ml at week 20 in adjusted model with p=0·007, comparing to Bonferroni correction alpha=0·05/6=0·0083.

Table S57. P-values for pairwise comparisons between conditions at each time point for cigarettes smoked per day using intent-to-treat method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·64	..		
8 mg/ml	0·23	0·46	..	
36 mg/ml	0·49	0·25	0·06	..
Week 1				
CS	..			
0 mg/ml	0·04	..		
8 mg/ml	0·01	0·70	..	
36 mg/ml	0·0003	0·14	0·27	..
Week 2				
CS	..			
0 mg/ml	0·01	..		
8 mg/ml	0·01[S]	0·80	..	
36 mg/ml	<0·0001	0·12	0·19	..
Week 4				
CS	..			
0 mg/ml	0·001	..		
8 mg/ml	0·0008	0·93	..	
36 mg/ml	<0·0001	0·30	0·34	..
Week 8				
CS	..			
0 mg/ml	0·002	..		
8 mg/ml	0·001	0·91	..	
36 mg/ml	<0·0001	0·27	0·32	..
Week 12				
CS	..			
0 mg/ml	0·04	..		
8 mg/ml	0·01[S]	0·51	..	
36 mg/ml	<0·001	0·05	0·20	..
Week 16				
CS	..			
0 mg/ml	0·01[S]	..		
8 mg/ml	0·02	0·64	..	
36 mg/ml	<0·0001	0·08	0·02	..

Week 20				
CS	..			
0 mg/ml	0·05	..		
8 mg/ml	0·003	0·37	..	
36 mg/ml	<0·0001	0·01	0·10	..
Week 24				
CS	..			
0 mg/ml	0·01	..		
8 mg/ml	0·002	0·59	..	
36 mg/ml	<0·0001	0·07	0·20	..
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·91	..		
8 mg/ml	0·41	0·48	..	
36 mg/ml	0·78	0·70	0·28	..
Week 1				
CS	..			
0 mg/ml	0·0007	..		
8 mg/ml	<0·0001	0·39	..	
36 mg/ml	<0·0001	0·38	0·99	..
Week 2				
CS	..			
0 mg/ml	0·0002	..		
8 mg/ml	<0·0001	0·48	..	
36 mg/ml	<0·0001	0·23	0·62	..
Week 4				
CS	..			
0 mg/ml	<0·0001	..		
8 mg/ml	<0·0001	0·59	..	
36 mg/ml	<0·0001	0·49	0·88	..
Week 8				
CS	..			
0 mg/ml	<0·0001	..		
8 mg/ml	<0·0001	0·89	..	
36 mg/ml	<0·0001	0·66	0·56	..
Week 12				
CS	..			

0 mg/ml	0·002	··		
8 mg/ml	<0·0001	0·30	··	
36 mg/ml	<0·0001	0·10	0·56	··
Week 16				
CS	··			
0 mg/ml	0·0001	··		
8 mg/ml	0·002	0·48	··	
36 mg/ml	<0·0001	0·16	0·034	··
Week 20				
CS	··			
0 mg/ml	0·01[S]	··		
8 mg/ml	<0·0001	0·28	··	
36 mg/ml	<0·0001	0·02	0·18	··
Week 24				
CS	··			
0 mg/ml	0·0009	··		
8 mg/ml	<0·0001	0·50	··	
36 mg/ml	<0·0001	0·09	0·32	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0.008, between all conditions.

S Significant difference between cigarette substitute and 8 mg/ml at week 2 in unadjusted model with p=0·005; significant difference between cigarette substitute and 8 mg/ml at week 12 in unadjusted model with p=0·005; significant difference between cigarette substitute and 0 mg/ml at week 16 in unadjusted model with p=0·006; significant difference between cigarette substitute and 0 mg/ml at week 20 in adjusted model with p=0·005, comparing to Bonferroni correction alpha=0·05/6=0·0083.

Table S58. P-values for pairwise comparisons between conditions at each time point for cigarettes smoked per day using per-protocol method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·82	..		
8 mg/ml	0·95	0·87	..	
36 mg/ml	0·28	0·43	0·34	..
Week 1				
CS	..			
0 mg/ml	0·01	..		
8 mg/ml	0·01	0·90	..	
36 mg/ml	0·01[S]	0·83	0·94	..
Week 2				
CS	..			
0 mg/ml	0·004	..		
8 mg/ml	0·003	0·97	..	
36 mg/ml	0·0003	0·57	0·60	..
Week 4				
CS	..			
0 mg/ml	0·0009	..		
8 mg/ml	0·0003	0·76	..	
36 mg/ml	<0·0001	0·66	0·89	..
Week 8				
CS	..			
0 mg/ml	0·002	..		
8 mg/ml	0·0007	0·80	..	
36 mg/ml	<0·0001	0·46	0·64	..
Week 12				
CS	..			
0 mg/ml	0·02	..		
8 mg/ml	0·01[S]	0·68	..	
36 mg/ml	<0·0001	0·14	0·29	..
Week 16				
CS	..			
0 mg/ml	0·002	..		
8 mg/ml	0·01	0·56	..	
36 mg/ml	<0·0001	0·18	0·05	..

Week 20				
CS	..			
0 mg/ml	0·01	..		
8 mg/ml	0·002	0·57	..	
36 mg/ml	<0·0001	0·031	0·12	..
Week 24				
CS	..			
0 mg/ml	0·01[S]	..		
8 mg/ml	0·002	0·71	..	
36 mg/ml	<0·0001	0·11	0·23	..
Adjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·86	..		
8 mg/ml	0·75	0·64	..	
36 mg/ml	0·54	0·69	0·38	..
Week 1				
CS	..			
0 mg/ml	0·004	..		
8 mg/ml	0·004	0·94	..	
36 mg/ml	0·01[S]	0·82	0·76	..
Week 2				
CS	..			
0 mg/ml	0·001	..		
8 mg/ml	0·001	0·99	..	
36 mg/ml	<0·0001	0·69	0·68	..
Week 4				
CS	..			
0 mg/ml	0·0001	..		
8 mg/ml	<0·0001	0·54	..	
36 mg/ml	<0·0001	0·68	0·81	..
Week 8				
CS	..			
0 mg/ml	0·0001	..		
8 mg/ml	0·0001	0·95	..	
36 mg/ml	<0·0001	0·71	0·77	..
Week 12				
CS	..			

0 mg/ml	0·01[S]	··		
8 mg/ml	0·001	0·57	··	
36 mg/ml	<0·0001	0·14	0·40	··
Week 16				
CS	··			
0 mg/ml	0·0002	··		
8 mg/ml	0·01	0·31	··	
36 mg/ml	<0·0001	0·23	0·03	··
Week 20				
CS	··			
0 mg/ml	0·002	··		
8 mg/ml	0·0004	0·63	··	
36 mg/ml	<0·0001	0·03	0·10	··
Week 24				
CS	··			
0 mg/ml	0·001	··		
8 mg/ml	0·0003	0·65	··	
36 mg/ml	<0·0001	0·10	0·27	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0.008, between all conditions.

S Significant difference between cigarette substitute and 36 mg/ml at week 1 in unadjusted model with p=0·005; significant difference between cigarette substitute and 8 mg/ml at week 12 in unadjusted model with p=0·005; significant difference between cigarette substitute and 0 mg/ml at week 24 in unadjusted model with p=0·007; significant difference between cigarette substitute and 36 mg/ml at week 1 in adjusted model with p=0·006; significant difference between cigarette substitute and 0 mg/ml at week 12 in adjusted model, p=0·0076, comparing to Bonferroni correction alpha=0·05/6=0·0083.

Table S59. P-values for pairwise comparisons between conditions at each time point for cigarettes smoked per day using baseline-carried-forward method

Unadjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·70	..		
8 mg/ml	0·31	0·54	..	
36 mg/ml	0·57	0·34	0·11	..
Week 1				
CS	..			
0 mg/ml	0·19	..		
8 mg/ml	0·08	0·67	..	
36 mg/ml	0·004	0·12	0·25	..
Week 2				
CS	..			
0 mg/ml	0·13	..		
8 mg/ml	0·06	0·73	..	
36 mg/ml	0·001	0·08	0·17	..
Week 4				
CS	..			
0 mg/ml	0·22	..		
8 mg/ml	0·05	0·46	..	
36 mg/ml	0·001	0·05	0·22	..
Week 8				
CS	..			
0 mg/ml	0·13	..		
8 mg/ml	0·17	0·90	..	
36 mg/ml	0·002	0·10	0·08	..
Week 12				
CS	..			
0 mg/ml	0·60	..		
8 mg/ml	0·37	0·71	..	
36 mg/ml	0·004	0·02	0·04	..
Week 16				
CS	..			
0 mg/ml	0·63	..		
8 mg/ml	0·68	0·94	..	
36 mg/ml	0·01[S]	0·03	0·03	..
Week 20				

CS	..			
0 mg/ml	0·75	..		
8 mg/ml	0·97	0·71	..	
36 mg/ml	0·02	0·01[S]	0·02	..
Week 24				
CS	..			
0 mg/ml	0·95	..		
8 mg/ml	0·95	1·00	..	
36 mg/ml	0·03	0·02	0·02	..
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·92	..		
8 mg/ml	0·68	0·61	..	
36 mg/ml	0·98	0·94	0·66	..
Week 1				
CS	..			
0 mg/ml	0·01	..		
8 mg/ml	0·0003	0·32	..	
36 mg/ml	0·0006	0·44	0·81	..
Week 2				
CS	..			
0 mg/ml	0·01[S]	..		
8 mg/ml	0·0001	0·29	..	
36 mg/ml	<0·0001	0·19	0·82	..
Week 4				
CS	..			
0 mg/ml	0·01[S]	..		
8 mg/ml	0·0001	0·22	..	
36 mg/ml	<0·0001	0·12	0·77	..
Week 8				
CS	..			
0 mg/ml	0·001	..		
8 mg/ml	0·003	0·82	..	
36 mg/ml	<0·0001	0·48	0·36	..
Week 12				
CS	..			
0 mg/ml	0·18	..		

8 mg/ml	0·04	0·47	··	
36 mg/ml	0·001	0·07	0·28	··
Week 16				
CS	··			
0 mg/ml	0·14	··		
8 mg/ml	0·22	0·82	··	
36 mg/ml	0·003	0·15	0·10	··
Week 20				
CS	··			
0 mg/ml	0·84	··		
8 mg/ml	0·44	0·57	··	
36 mg/ml	0·01	0·02	0·08	··
Week 24				
CS	··			
0 mg/ml	0·59	··		
8 mg/ml	0·56	0·96	··	
36 mg/ml	0·02	0·07	0·08	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·008, between all conditions.

S Significant difference between cigarette substitute and 36 mg/ml at week 16 in unadjusted model, p=0·0078; significant difference between 0 mg/ml and 36 mg/ml at week 20 in unadjusted model with p=0·0082; significant difference between cigarette substitute and 36 mg/ml at week 2 in adjusted model, p=0·006; significant difference between cigarette substitute and 0 mg/ml at week 4 in adjusted model, p-value=0·00803. All compared to Bonferroni correction alpha=0·05/6=0·00833.

Table S60. P-values for pairwise comparisons between conditions at each time point for cigarettes smoked per day using last-observation-carried-forward method

Unadjusted Model*				
Week 0				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
CS	..			
0 mg/ml	0·66	..		
8 mg/ml	0·26	0·49	..	
36 mg/ml	0·52	0·28	0·08	..
Week 1				
CS	..			
0 mg/ml	0·15	..		
8 mg/ml	0·05	0·64	..	
36 mg/ml	0·001	0·08	0·20	..
Week 2				
CS	..			
0 mg/ml	0·08	..		
8 mg/ml	0·02	0·56	..	
36 mg/ml	0·0003	0·06	0·19	..
Week 4				
CS	..			
0 mg/ml	0·03	..		
8 mg/ml	0·004	0·50	..	
36 mg/ml	<0·0001	0·07	0·27	..
Week 8				
CS	..			
0 mg/ml	0·04	..		
8 mg/ml	0·01[S]	0·44	..	
36 mg/ml	0·0001	0·07	0·30	..
Week 12				
CS	..			
0 mg/ml	0·18	..		
8 mg/ml	0·01	0·25	..	
36 mg/ml	0·0001	0·01	0·17	..
Week 16				
CS	..			
0 mg/ml	0·11	..		
8 mg/ml	0·04	0·64	..	
36 mg/ml	<0·0001	0·01	0·04	..
Week 20				

CS	..			
0 mg/ml	0·27	..		
8 mg/ml	0·01	0·16	..	
36 mg/ml	<0·0001	0·002	0·09	..
Week 24				
CS	..			
0 mg/ml	0·22	..		
8 mg/ml	0·01	0·21	..	
36 mg/ml	<0·0001	0·01[S]	0·13	..
Adjusted Model*				
Week 0				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
CS	..			
0 mg/ml	0·95	..		
8 mg/ml	0·47	0·51	..	
36 mg/ml	0·83	0·79	0·36	..
Week 1				
CS	..			
0 mg/ml	0·01	..		
8 mg/ml	0·0005	0·37	..	
36 mg/ml	0·0002	0·25	0·82	..
Week 2				
CS	..			
0 mg/ml	0·01[S]	..		
8 mg/ml	<0·0001	0·27	..	
36 mg/ml	<0·0001	0·13	0·72	..
Week 4				
CS	..			
0 mg/ml	0·0005	..		
8 mg/ml	<0·0001	0·20	..	
36 mg/ml	<0·0001	0·13	0·84	..
Week 8				
CS	..			
0 mg/ml	0·0003	..		
8 mg/ml	<0·0001	0·30	..	
36 mg/ml	<0·0001	0·22	0·86	..
Week 12				
CS	..			
0 mg/ml	0·02	..		

8 mg/ml	<0·0001	0·06	··	
36 mg/ml	<0·0001	0·02	0·72	··
Week 16				
CS	··			
0 mg/ml	0·01[S]	··		
8 mg/ml	0·0004	0·45	··	
36 mg/ml	<0·0001	0·02	0·14	··
Week 20				
CS	··			
0 mg/ml	0·02	··		
8 mg/ml	<0·0001	0·05	··	
36 mg/ml	<0·0001	0·003	0·34	··
Week 24				
CS	··			
0 mg/ml	0·02	··		
8 mg/ml	<0·0001	0·06	··	
36 mg/ml	<0·0001	0·01	0·50	··

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·008, between all conditions.

S Significant difference between cigarette substitute and 8 mg/ml at week 8 in unadjusted model, p=0·005; significant difference between 0 mg/ml and 36 mg/ml at week 24 in unadjusted model, p=0·006; significant difference between cigarette substitute and 0 mg/ml at week 2 in adjusted model with p=0·005; significant difference between cigarette substitute and 0 mg/ml at week 16 in adjusted model with p=0·005. All compared to Bonferroni correction alpha=0·05/6=0·00833.

Table S61. P-values for pairwise comparisons relative to baseline within each condition for cigarettes smoked per day using multiple imputation method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

Table S62. P-values for pairwise comparisons relative to baseline within each condition for cigarettes smoked per day using intent-to-treat method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

Table S63. P-values for pairwise comparisons relative to baseline within each condition for cigarettes smoked per day using per-protocol method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

Table S64. P-values for pairwise comparisons relative to baseline within each condition for cigarettes smoked per day using baseline-carried-forward method

Unadjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001
Adjusted Model*				
	CS	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

Table S65. P-values for pairwise comparisons relative to baseline within each condition for cigarettes smoked per day using last-observation-carried-forward method

Unadjusted Model*				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001
Adjusted Model*				
	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 1	<0·0001	<0·0001	<0·0001	<0·0001
Week 2	<0·0001	<0·0001	<0·0001	<0·0001
Week 4	<0·0001	<0·0001	<0·0001	<0·0001
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001

Note: CS, cigarette substitute. The adjusted model included the following covariates: site, gender, age, race/ethnicity, week 0 exhaled CO, week 0 cigarettes smoked per day, education level, week 0 Kessler K6 score, week 0 Penn State Cigarette Dependence Index score, and week 0 forced expiratory volume in one second.

* Bonferroni correction alpha=0·006, relative to baseline (week 0).

Table S66. Study product use percentages using intent-to-treat method (with assumption of no use to missing study product usage logs)

Percent using study product, %, (n)	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 1	86·92 (113)	85·38 (111)	87·69 (114)	89·23 (116)
Week 2	77·69 (101)	75·38 (98)	84·62 (110)	84·62 (110)
Week 4	71·54 (93)	66·92 (87)	75·38 (98)	81·54 (106)
Week 8	44·62 (58)	54·62 (71)	56·92 (74)	60·77 (79)
Week 12	41·54 (54)	42·31 (55)	52·31 (68)	55·38 (72)
Week 16	34·62 (45)	43·08 (56)	43·85 (57)	53·85 (70)
Week 20	36·15 (47)	35·38 (46)	40·77 (53)	48·46 (63)
Week 24	33·08 (43)	36·15 (47)	37·69 (49)	47·69 (62)

Note: CS, cigarette substitute. Participants with missing study product usage logs were assumed no use of study product. Denominator for calculating the percent using is always 130 for every condition.

Table S67. Study product use percentages using intent-to-treat method (with no assumption on missing study product usage logs)

Percent using study product, %, (n)	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 1	93·39 (113)	99·11 (111)	98·28 (114)	96·67 (116)
Week 2	87·83 (101)	94·23 (98)	94·83 (110)	97·35 (110)
Week 4	80·87 (93)	90·63 (87)	89·09 (98)	94·64 (106)
Week 8	61·05 (58)	84·52 (71)	80·43 (74)	83·16 (79)
Week 12	58·70 (54)	70·51 (55)	80·00 (68)	77·42 (72)
Week 16	52·33 (45)	78·87 (56)	73·08 (57)	83·33 (70)
Week 20	54·65 (47)	70·77 (46)	73·61 (53)	80·77 (63)
Week 24	47·25 (43)	68·12 (47)	66·22 (49)	77·50(62)

Note: CS, cigarette substitute. Denominator for calculating the percent using is based on number of participants who reported study product usage and is varied by weeks and conditions.

Table S68. Study product use percentages using per-protocol method

Percent using study product, %, (n)	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 1	92·86 (78)	98·46 (64)	100 (64)	96·15 (75)
Week 2	84·52 (71)	95·45 (63)	95·52 (64)	98·72 (77)
Week 4	77·91 (67)	94·03 (63)	89·55 (60)	97·47 (77)
Week 8	58·75 (47)	86·36 (57)	80·30 (53)	86·67 (65)
Week 12	59·30 (51)	71·64 (48)	80·60 (54)	79·75 (63)
Week 16	50·62 (41)	79·69 (51)	73·44 (47)	84·42 (65)
Week 20	54·32 (44)	72·13 (44)	73·85 (48)	80·52 (62)
Week 24	47·67 (41)	67·16 (45)	65·67 (44)	77·22 (61)

Note: CS, cigarette substitute. Participants with missing study product usage logs were assumed no use of study product. Study sample for pre-protocol method is based on participants who completed weeks 0, 4, 12 and 24. The sample sizes for each condition are CS, N=86; 0 mg/ml, N=67; 8 mg/ml, N=67; 36 mg/ml, N=79, respectively. Participants may be missing study product usage logs at different visits other than weeks 0, 4, 12 and 24. Denominator for calculating the percent using is based on number of participants who reported study product usage and is varied by weeks and conditions.

Table S69. P-values of between-condition comparisons for study product use percentages using intent-to-treat method (with assumption of no use to missing study product usage logs)

	CS-0 mg/ml	CS-8 mg/ml	CS-36 mg/ml	0 mg/ml-8 mg/ml	0 mg/ml-36 mg/ml	8 mg/ml-36 mg/ml
Week 1	0·72	0·85	0·57	0·59	0·35	0·70
Week 2	0·66	0·15	0·15	0·06	0·06	1·00
Week 4	0·42	0·48	0·06	0·13	0·01 [S]	0·23
Week 8	0·11	0·05	0·01	0·71	0·32	0·53
Week 12	0·90	0·08	0·03	0·11	0·04	0·62
Week 16	0·16	0·13	0·002	0·90	0·08	0·11
Week 20	0·90	0·44	0·05	0·37	0·03	0·21
Week 24	0·60	0·44	0·02	0·80	0·06	0·10

Note: CS, cigarette substitute. Participants with missing study product usage logs were assumed no use of study product. Unless otherwise indicated, Chi-square tests were used. Bonferroni correction alpha=0·008, between conditions comparisons.

S Significant difference between 0 mg/ml and 36 mg/ml at week 4 with p=0·007, comparing to Bonferroni correction alpha=0·05/6=0·0083.

Table S70. P-values of between-condition comparisons for study product use percentages using intent-to-treat method (with no assumption on missing study product usage logs)

	CS-0 mg/ml	CS-8 mg/ml	CS-36 mg/ml	0 mg/ml-8 mg/ml	0 mg/ml-36 mg/ml	8 mg/ml-36 mg/ml
Week 1	0·04*	0·10*	0·24	1·00*	0·37*	0·68*
Week 2	0·10	0·06	0·01 [S]	0·85	0·32*	0·50*
Week 4	0·05	0·09	0·002	0·72	0·26	0·13
Week 8	0·0005	0·004	0·001	0·48	0·80	0·63
Week 12	0·11	0·002	0·01 [S]	0·16	0·30	0·67
Week 16	0·0005	0·01 [S]	<0·0001	0·41	0·48	0·11
Week 20	0·04	0·01	0·0004	0·71	0·16	0·30
Week 24	0·01	0·02	<0·0001	0·81	0·20	0·12

Note: CS, cigarette substitute. Unless otherwise indicated, Chi-square tests were used. Bonferroni correction alpha=0·008, between conditions comparisons.

S Significant difference between cigarette substitute and 8 mg/ml at week 16 with p=0·006; significant difference between cigarette substitute and 36 mg/ml at week 2 with p=0·006; significant difference between cigarette substitute and 36 mg/ml at week 12 with p=0·006, comparing to Bonferroni correction alpha=0·05/6=0·0083.

* Based on Fisher's Exact tests.

Table S71. P-values of between-condition comparisons for study product use percentages using per-protocol method

	CS-0 mg/ml	CS-8 mg/ml	CS-36 mg/ml	0 mg/ml-8 mg/ml	0 mg/ml-36 mg/ml	8 mg/ml-36 mg/ml
Week 1	0·14*	0·04*	0·50*	1·00*	0·63*	0·25*
Week 2	0·03	0·03	0·001	1·00*	0·33*	0·34*
Week 4	0·01 S	0·06	0·0002	0·35	0·41*	0·08*
Week 8	0·0002	0·01 S	0·0001	0·35	0·96	0·31
Week 12	0·11	0·01 S	0·01 S	0·22	0·25	0·90
Week 16	0·0003	0·01 S	<0·0001	0·40	0·46	0·11
Week 20	0·03	0·02	0·0005	0·83	0·25	0·34
Week 24	0·02	0·03	<0·0001	0·85	0·17	0·12

Note: CS, cigarette substitute. Unless otherwise indicated, Chi-square tests were used. Bonferroni correction alpha=0·008, between conditions comparisons.

S Significant difference between cigarette substitute and 0 mg/ml at week 4 with p=0·006; significant differences between cigarette substitute and 8 mg/ml at week 2, 12, and 16, each p=0·005; significant difference between cigarette substitute and 36 mg/ml at week 12 with p=0·005, comparing to Bonferroni correction alpha=0·05/6=0·0083.

* Based on Fisher's Exact tests.

Table S72. P-values of relative to week 1 comparisons for study product use percentages using intent-to-treat method (with assumption of no use to missing study product usage logs)

	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 2	0·05	0·04	0·47	0·27
Week 4	0.002	0.0005	0.01	0.08
Week 8	<0·0001	<0·0001	<0·0001	<0·0001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	<0·0001
Week 20	<0·0001	<0·0001	<0·0001	<0·0001
Week 24	<0·0001	<0·0001	<0·0001	<0·0001

Note: CS, cigarette substitute. Unless otherwise indicated, Chi-square tests were used. Bonferroni correction alpha=0·007, relative to week 1 comparisons.

Table S73. P-values of relative to week 1 comparisons for study product use percentages using intent-to-treat method (with no assumption of no use to missing study product usage logs)

	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 2	0·14	0·06*	0·28*	1·00
Week 4	0·004	0·006*	0·004	0·53*
Week 8	<0·0001	<0·0001	<0·0001	0·001
Week 12	<0·0001	<0·0001	<0·0001	<0·0001
Week 16	<0·0001	<0·0001	<0·0001	0·001
Week 20	<0·0001	<0·0001	<0·0001	0·0002
Week 24	<0·0001	<0·0001	<0·0001	<0·0001

Note: CS, cigarette substitute. Unless otherwise indicated, Chi-square tests were used. Bonferroni correction alpha=0·007, relative to week 1 comparisons.

* Based on Fisher's Exact tests.

Table S74. P-values of relative to week 1 comparisons for study product use percentages using per-protocol method

	CS	0 mg/ml	8 mg/ml	36 mg/ml
Week 2	0·09	0·62*	0·24*	0·62*
Week 4	0·006	0·37*	0·01*	0·68*
Week 8	<0·0001	0·02*	0·0002	0·04
Week 12	<0·0001	<0·0001	0·0002	0·002
Week 16	<0·0001	0·0006	<0·0001	0·01
Week 20	<0·0001	<0·0001	<0·0001	0·002
Week 24	<0·0001	<0·0001	<0·0001	0·0005

Note: CS, cigarette substitute. Unless otherwise indicated, Chi-square tests were used. Bonferroni correction alpha=0·007, relative to week 1 comparisons.

* Based on Fisher's Exact tests.

Table S75. Summary of adverse events

Description			Week 0, Baseline				Week 1 - Week 24, Intervention Period				Week 25 - Week 36, Follow-up Period			
	Overall	Pre*	CS	0 mg/ml	8 mg/ml	36 mg/ml	CS	0 mg/ml	8 mg/ml	36 mg/ml	CS	0 mg/ml	8 mg/ml	36 mg/ml
Total events (per symptom)	1185	5	82	84	80	83	135	169	213	228	26	27	26	27
Abdominal pain	7	0	0	0	0	0	1	3	2	1	0	0	0	0
Adrenal insufficiency	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Allergic reaction	8	0	0	0	1	0	1	1	2	3	0	0	0	0
Allergic rhinitis	7	0	0	0	0	0	0	2	2	3	0	0	0	0
Anaphylaxis	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Ankle fracture	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Anxiety	19	0	0	0	0	0	3	4	5	5	1	0	0	1
Appendicitis/Appendicitis perforated	3	0	0	0	0	0	0	0	2	1	0	0	0	0
Arthragia	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Arthritis	4	0	0	0	0	0	2	1	1	0	0	0	0	0
Aspartate aminotransferase increased	2	0	0	0	1	1	0	0	0	0	0	0	0	0
Aspiration	3	0	0	0	0	0	2	0	0	1	0	0	0	0
Back pain	25	0	0	0	0	1	4	3	4	9	2	1	1	0
Bladder infection	2	0	0	0	0	0	1	0	1	0	0	0	0	0
Bloating	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Blood and lymphatic system disorders - Other, specify	2	0	0	0	1	1	0	0	0	0	0	0	0	0
Blurred vision	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Bone pain	2	0	0	0	0	0	0	1	0	0	1	0	0	0
Bronchial infection	15	0	0	0	0	1	2	3	4	0	1	1	0	3
Bruising	2	0	0	0	0	0	2	0	0	0	0	0	0	0
Burn	2	0	0	1	0	0	0	0	1	0	0	0	0	0
Cardiac disorders - Other, specify	5	0	0	0	0	0	0	1	0	1	0	1	0	2
Chest pain - cardiac	7	0	0	0	0	0	2	1	1	2	0	1	0	0
Chest wall pain	2	0	0	0	0	0	0	0	1	1	0	0	0	0
Cholesterol high	9	0	0	2	1	3	1	0	1	0	0	0	1	0
Chronic kidney disease	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Colonic obstruction	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Conjunctivitis	1	0	0	0	0	0	0	0	0	1	0	0	0	0

Constipation	4	0	0	1	0	0	1	0	1	1	0	0	0	0
Cough	35	0	0	1	2	0	3	6	14	9	0	0	0	0
Creatinine increased	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Death-not otherwise specified	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Dehydration	3	0	0	0	0	0	2	0	1	0	0	0	0	0
Depressed level of consciousness	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Depressed mood	9	0	1	0	0	0	2	2	1	3	0	0	0	0
Depression	14	0	0	0	0	0	3	4	4	1	0	1	0	1
Diarrhea	3	0	0	0	0	0	0	1	1	0	0	0	0	1
Dizziness	8	0	1	0	0	0	1	3	2	1	0	0	0	0
Dry cough	21	0	0	0	0	0	0	4	9	8	0	0	0	0
Dry mouth	6	0	0	0	0	0	0	1	2	3	0	0	0	0
Dry skin	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Dyspnea	5	0	0	0	0	0	0	2	1	1	0	1	0	0
Ear and labyrinth disorders - Other, specify	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Edema limbs	2	0	0	0	0	0	0	0	1	1	0	0	0	0
Epistaxis	2	0	0	0	0	0	0	0	1	1	0	0	0	0
Eye disorders - Other, specify	3	1	0	0	0	0	0	0	1	0	0	1	0	0
Fall	5	1	0	0	0	0	1	1	2	0	0	0	0	0
Fatigue	4	0	1	0	0	0	1	0	2	0	0	0	0	0
Fever	4	0	0	0	1	0	0	0	1	2	0	0	0	0
Flu like symptoms	33	0	1	0	0	2	6	7	8	7	1	1	0	0
Fracture	9	0	0	0	1	0	0	1	0	2	2	0	0	3
Gastric ulcer	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Gastritis	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Gastroesophageal reflux disease	2	0	0	0	0	0	0	0	0	2	0	0	0	0
Gastrointestinal disorders - Other, specify	8	0	0	0	0	0	2	0	2	4	0	0	0	0
Gastrointestinal pain	2	0	0	0	0	0	0	0	2	0	0	0	0	0
General disorders and administration site conditions - Other, specify	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Generalized muscle weakness	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Gum infection	2	0	0	0	0	0	0	1	0	0	0	0	1	0

Hallucinations	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Headache	31	0	0	0	0	0	2	9	10	10	0	0	0	0
Heart failure	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Hepatobiliary disorders	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Hepatobiliary disorders - other	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Hiccups	2	0	0	0	0	0	0	0	0	2	0	0	0	0
Hyperglycemia	2	0	0	0	1	0	0	0	0	0	0	0	1	0
Hyperkalemia	3	0	1	1	1	0	0	0	0	0	0	0	0	0
Hypertension	50	0	2	4	3	3	6	10	8	9	2	1	1	1
Hypertriglyceridemia	12	0	2	3	2	3	0	0	1	1	0	0	0	0
Hypocalcemia	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Hypoglycemia	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Hyponatremia	1	0	0	1	0	0	0	0	0	0	0	0	0	0
Increased appetite	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Infections and infestations - Other, specify	7	0	0	0	0	0	1	1	1	3	0	1	0	0
Injury, poisoning and procedural complications	5	0	0	1	0	0	0	1	1	1	0	0	1	0
Injury, poisoning and procedural complications - Other, specify	20	0	0	0	0	0	5	1	6	4	2	0	2	0
Investigations - Other, specify	10	0	2	1	2	3	0	2	0	0	0	0	0	0
Irritability	5	0	0	0	0	0	2	0	2	1	0	0	0	0
Joint range of motion decreased	2	0	0	0	0	0	1	1	0	0	0	0	0	0
Laryngitis	2	0	0	0	0	0	1	0	0	1	0	0	0	0
Lethargy	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Leukocytosis	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Lung infection	2	0	0	1	0	0	0	0	0	0	1	0	0	0
Lymph node pain	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Metabolism and nutrition disorders - Other, specify	2	0	0	0	0	0	0	0	1	1	0	0	0	0
Mitral valve disease	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Mouth ulcers	16	0	1	0	0	0	0	3	6	5	1	0	0	0
Mucus in throat/sinus	5	0	0	0	1	0	0	3	1	0	0	0	0	0
Musculoskeletal and connective tissue disorder - Other, specify	6	0	0	0	0	0	1	0	4	1	0	0	0	0
Musculoskeletal deformity	1	0	0	0	0	0	0	1	0	0	0	0	0	0

Myocardial infarction	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Nasal congestion	34	0	1	0	0	2	6	5	7	9	0	0	2	2
Nausea	19	0	0	0	0	0	2	2	7	6	1	0	1	0
Neck pain	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps) - Other, specify	7	0	0	0	0	0	1	1	1	1	0	2	0	1
Nervous system disorders - Other, specify	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Non-cardiac chest pain	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Non-MedDRA - Bad taste resulting from dry puff	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Oral pain	7	1	0	0	0	0	1	1	2	0	1	0	0	1
Pain	20	0	0	1	0	0	6	2	3	6	0	1	1	0
Pain in extremity	6	0	0	0	0	0	2	1	2	0	0	0	1	0
Palpitations	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Paresthesia	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Pharyngitis	3	0	0	0	0	0	2	0	1	0	0	0	0	0
Pneumonitis	3	0	0	0	0	0	1	0	0	2	0	0	0	0
Productive cough	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Prostate infection	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Pruritus	1	0	0	0	0	1	0	0	0	0	0	0	0	0
Psychiatric disorders - Other, specify	8	0	0	0	0	0	2	0	3	2	0	0	1	0
Rash	2	0	0	0	0	0	0	0	2	0	0	0	0	0
Rectal obstruction	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Reproductive system and breast disorders - Other, specify	5	0	0	0	0	0	1	0	1	2	0	1	0	0
Respiratory, thoracic and mediastinal disorders - Other, specify	339	0	62	63	59	61	22	16	15	26	3	7	4	1
Rhinitis	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Seizure	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Shortness of breath	3	0	0	0	0	0	1	1	1	0	0	0	0	0
Sinus disorder	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Sinus pain	2	0	0	0	0	0	0	1	1	0	0	0	0	0
Sinus tachycardia	2	0	0	0	0	0	0	1	1	0	0	0	0	0
Sinusitis	16	0	1	0	0	0	3	3	5	1	0	1	1	1

Skin and subcutaneous tissue disorders - Other, specify	7	0	1	0	0	0	1	2	2	1	0	0	0	0
Skin infection	2	0	0	0	0	0	0	0	0	1	0	1	0	0
Sore throat	27	0	1	0	0	0	0	7	6	11	1	0	1	0
Stomach pain	2	0	0	0	0	0	1	1	0	0	0	0	0	0
Stroke	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Suicidal ideation	2	0	0	0	0	0	0	1	0	0	0	1	0	0
Suicide attempt	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Surgical and medical procedures - Other, specify	46	0	0	0	0	0	7	10	7	14	2	1	4	1
Syncope	2	0	0	0	0	1	0	1	0	0	0	0	0	0
Throat irritation	4	0	0	0	0	0	0	1	1	2	0	0	0	0
Tooth infection	5	0	0	0	0	0	1	4	0	0	0	0	0	0
Toothache	11	0	0	0	1	0	2	3	2	1	1	1	0	0
Tremor	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Upper respiratory infection	49	1	1	3	1	0	4	10	13	13	1	0	1	1
Urinary tract infection	4	0	0	0	0	0	2	0	1	1	0	0	0	0
Vomiting	4	0	0	0	0	0	1	1	0	1	0	0	0	1
Watering eyes	2	0	0	0	0	0	0	1	0	1	0	0	0	0
Wheezing	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Wound infection	1	0	0	0	0	0	0	0	0	1	0	0	0	0

Note: CS, cigarette substitute.

*Pre-randomisation

Table S76. Number of participants with an event

Description			Week 0, Baseline				Week 1 - Week 24, Intervention Period				Week 25 - Week 36, Follow-up Period			
	Overall	Pre*	CS	0 mg/ml	8 mg/ml	36 mg/ml	CS	0 mg/ml	8 mg/ml	36 mg/ml	CS	0 mg/ml	8 mg/ml	36 mg/ml
Total number of participant-events	1159	5	81	81	80	83	130	164	208	222	26	26	26	27
Abdominal pain	7	0	0	0	0	0	1	3	2	1	0	0	0	0
Adrenal insufficiency	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Allergic reaction	7	0	0	0	1	0	1	1	1	3	0	0	0	0
Allergic rhinitis	7	0	0	0	0	0	0	2	2	3	0	0	0	0
Anaphylaxis	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Ankle fracture	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Anxiety	18	0	0	0	0	0	2	4	5	5	1	0	0	1
Appendicitis/Appendicitis perforated	3	0	0	0	0	0	0	0	2	1	0	0	0	0
Arthragia	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Arthritis	4	0	0	0	0	0	2	1	1	0	0	0	0	0
Aspartate aminotransferase increased	2	0	0	0	1	1	0	0	0	0	0	0	0	0
Aspiration	3	0	0	0	0	0	2	0	0	1	0	0	0	0
Back pain	25	0	0	0	0	1	4	3	4	9	2	1	1	0
Bladder infection	2	0	0	0	0	0	1	0	1	0	0	0	0	0
Bloating	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Blood and lymphatic system disorders - Other, specify	2	0	0	0	1	1	0	0	0	0	0	0	0	0
Blurred vision	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Bone pain	2	0	0	0	0	0	0	1	0	0	1	0	0	0
Bronchial infection	15	0	0	0	0	1	2	3	4	0	1	1	0	3
Bruising	2	0	0	0	0	0	2	0	0	0	0	0	0	0
Burn	2	0	0	1	0	0	0	0	1	0	0	0	0	0
Cardiac disorders - Other, specify	5	0	0	0	0	0	0	1	0	1	0	1	0	2
Chest pain - cardiac	7	0	0	0	0	0	2	1	1	2	0	1	0	0
Chest wall pain	2	0	0	0	0	0	0	0	1	1	0	0	0	0

Cholesterol high	9	0	0	2	1	3	1	0	1	0	0	0	1	0
Chronic kidney disease	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Colonic obstruction	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Conjunctivitis	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Constipation	4	0	0	1	0	0	1	0	1	1	0	0	0	0
Cough	33	0	0	1	2	0	3	5	14	8	0	0	0	0
Creatinine increased	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Death NOS	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Dehydration	2	0	0	0	0	0	1	0	1	0	0	0	0	0
Depressed level of consciousness	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Depressed mood	9	0	1	0	0	0	2	2	1	3	0	0	0	0
Depression	14	0	0	0	0	0	3	4	4	1	0	1	0	1
Diarrhea	3	0	0	0	0	0	0	1	1	0	0	0	0	1
Dizziness	8	0	1	0	0	0	1	3	2	1	0	0	0	0
Dry cough	21	0	0	0	0	0	0	4	9	8	0	0	0	0
Dry mouth	6	0	0	0	0	0	0	1	2	3	0	0	0	0
Dry skin	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Dyspnea	5	0	0	0	0	0	0	2	1	1	0	1	0	0
Ear and labyrinth disorders - Other, specify	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Edema limbs	2	0	0	0	0	0	0	0	1	1	0	0	0	0
Epistaxis	2	0	0	0	0	0	0	0	1	1	0	0	0	0
Eye disorders - Other, specify	3	1	0	0	0	0	0	0	1	0	0	1	0	0
Fall	5	1	0	0	0	0	1	1	2	0	0	0	0	0
Fatigue	4	0	1	0	0	0	1	0	2	0	0	0	0	0
Fever	4	0	0	0	1	0	0	0	1	2	0	0	0	0
Flu like symptoms	33	0	1	0	0	2	6	7	8	7	1	1	0	0
Fracture	9	0	0	0	1	0	0	1	0	2	2	0	0	3
Gastric ulcer	1	0	0	0	0	0	0	0	0	0	1	0	0	0

Gastritis	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Gastroesophageal reflux disease	2	0	0	0	0	0	0	0	0	2	0	0	0	0
Gastrointestinal disorders - Other, specify	8	0	0	0	0	0	2	0	2	4	0	0	0	0
Gastrointestinal pain	2	0	0	0	0	0	0	0	2	0	0	0	0	0
General disorders and administration site conditions - Other, specify	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Generalized muscle weakness	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Gum infection	2	0	0	0	0	0	0	1	0	0	0	0	1	0
Hallucinations	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Headache	30	0	0	0	0	0	2	8	10	10	0	0	0	0
Heart failure	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Hepatobiliary disorders	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Hepatobiliary disorders - other	1	0	0	0	0	0	0	0	0	0	0	1	0	0
Hiccups	2	0	0	0	0	0	0	0	0	2	0	0	0	0
Hyperglycemia	2	0	0	0	1	0	0	0	0	0	0	0	1	0
Hyperkalemia	3	0	1	1	1	0	0	0	0	0	0	0	0	0
Hypertension	46	0	2	3	3	3	5	8	8	9	2	1	1	1
Hypertriglyceridemia	12	0	2	3	2	3	0	0	1	1	0	0	0	0
Hypocalcemia	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Hypoglycemia	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Hyponatremia	1	0	0	1	0	0	0	0	0	0	0	0	0	0
Increased appetite	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Infections and infestations - Other, specify	7	0	0	0	0	0	1	1	1	3	0	1	0	0
Injury, poisoning and procedural complications	5	0	0	1	0	0	0	1	1	1	0	0	1	0
Injury, poisoning and procedural complications - Other, specify	20	0	0	0	0	0	5	1	6	4	2	0	2	0
Investigations - Other, specify	10	0	2	1	2	3	0	2	0	0	0	0	0	0
Irritability	5	0	0	0	0	0	2	0	2	1	0	0	0	0
Joint range of motion decreased	2	0	0	0	0	0	1	1	0	0	0	0	0	0

Laryngitis	2	0	0	0	0	0	1	0	0	1	0	0	0	0
Lethargy	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Leukocytosis	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Lung infection	2	0	0	1	0	0	0	0	0	0	1	0	0	0
Lymph node pain	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Metabolism and nutrition disorders - Other, specify	2	0	0	0	0	0	0	0	1	1	0	0	0	0
Mitral valve disease	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Mouth ulcers	15	0	1	0	0	0	0	3	5	5	1	0	0	0
Mucus in throat/sinus	5	0	0	0	1	0	0	3	1	0	0	0	0	0
Musculoskeletal and connective tissue disorder - Other, specify	5	0	0	0	0	0	1	0	3	1	0	0	0	0
Musculoskeletal deformity	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Myocardial infarction	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Nasal congestion	33	0	1	0	0	2	6	5	7	8	0	0	2	2
Nausea	19	0	0	0	0	0	2	2	7	6	1	0	1	0
Neck pain	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	6	0	0	0	0	0	1	1	1	1	0	1	0	1
Nervous system disorders - Other, specify	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Non-cardiac chest pain	1	0	0	0	0	0	1	0	0	0	0	0	0	0
Non-MedDRA - Bad taste resulting from dry puff	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Oral pain	7	1	0	0	0	0	1	1	2	0	1	0	0	1
Pain	20	0	0	1	0	0	6	2	3	6	0	1	1	0
Pain in extremity	6	0	0	0	0	0	2	1	2	0	0	0	1	0
Palpitations	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Paresthesia	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Pharyngitis	3	0	0	0	0	0	2	0	1	0	0	0	0	0
Pneumonitis	3	0	0	0	0	0	1	0	0	2	0	0	0	0
Productive cough	1	0	0	0	0	0	0	0	1	0	0	0	0	0

Prostate infection	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Pruritus	1	0	0	0	0	1	0	0	0	0	0	0	0	0
Psychiatric disorders - Other, specify	8	0	0	0	0	0	2	0	3	2	0	0	1	0
Rash	2	0	0	0	0	0	0	0	2	0	0	0	0	0
Rectal obstruction	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Reproductive system and breast disorders - Other, specify	5	0	0	0	0	0	1	0	1	2	0	1	0	0
Respiratory, thoracic and mediastinal disorders - Other, specify	332	0	61	61	59	61	21	15	14	25	3	7	4	1
Rhinitis	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Seizure	1	0	0	0	1	0	0	0	0	0	0	0	0	0
Shortness of breath	3	0	0	0	0	0	1	1	1	0	0	0	0	0
Sinus disorder	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Sinus pain	2	0	0	0	0	0	0	1	1	0	0	0	0	0
Sinus tachycardia	2	0	0	0	0	0	0	1	1	0	0	0	0	0
Sinusitis	16	0	1	0	0	0	3	3	5	1	0	1	1	1
Skin and subcutaneous tissue disorders - Other, specify	7	0	1	0	0	0	1	2	2	1	0	0	0	0
Skin infection	2	0	0	0	0	0	0	0	0	1	0	1	0	0
Sore throat	27	0	1	0	0	0	0	7	6	11	1	0	1	0
Stomach pain	2	0	0	0	0	0	1	1	0	0	0	0	0	0
Stroke	1	0	0	0	0	0	0	0	1	0	0	0	0	0
Suicidal ideation	2	0	0	0	0	0	0	1	0	0	0	1	0	0
Suicide attempt	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Surgical and medical procedures - Other, specify	45	0	0	0	0	0	7	10	7	13	2	1	4	1
Syncope	2	0	0	0	0	1	0	1	0	0	0	0	0	0
Throat irritation	4	0	0	0	0	0	0	1	1	2	0	0	0	0
Tooth infection	5	0	0	0	0	0	1	4	0	0	0	0	0	0
Toothache	11	0	0	0	1	0	2	3	2	1	1	1	0	0
Tremor	1	0	0	0	0	0	0	0	0	0	0	0	0	1

Upper respiratory infection	46	1	1	3	1	0	4	10	12	11	1	0	1	1
Urinary tract infection	3	0	0	0	0	0	1	0	1	1	0	0	0	0
Vomiting	4	0	0	0	0	0	1	1	0	1	0	0	0	1
Watering eyes	2	0	0	0	0	0	0	1	0	1	0	0	0	0
Wheezing	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Wound infection	1	0	0	0	0	0	0	0	0	1	0	0	0	0

Note: CS, cigarette substitute.

*Pre-randomisation

Table S77. Count of serious and severe adverse events

		Baseline (W0)				Intervention Period (W1-W24)				Follow-up Period (W25-W36)			
	Overall	**CS**	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**	**CS**	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**	**CS**	**0 mg/ml**	**8 mg/ml**	**36 mg/ml**
Number of serious AEs	44*	0	1	1	0	11	7	5	8	2	3	1	4
Number of serious AEs (possible/probably/definitely related)ǂ	0	0	0	0	0	0	0	0	0	0	0	0	0
Number of severe AEs	114*	2	8	7	6	19	21	14	17	5	5	1	8
Number of severe AEs (possible/probable/definitely related)	4	0	0	0	0	0	1	2	1	0	0	0	0

Note: AE, adverse event; W, week. Multiple symptoms related to the same event in the same participant are only counted once. Study period (baseline, intervention, follow-up) when AE noted may represent when symptoms (i.e., initial AE) first emerged not when the serious and/or severe event was documented. Serious AEs may have been designated as either mild/moderate/severe/life-threatening/fatal in terms of severity. Severe AEs include those coded as severe/life-threatening/fatal.

ǂ All serious AEs are unrelated or unlikely (remote)

* One serious and severe AE happened at week 0 before randomisation hence is not categorized in any of the conditions

Table S78. Description of serious and severe events

Seriousness	Severity	Relatedness	Withdrawn	Condition	Description
Yes	Fatal	Unrelated	Yes-prior to randomisation	-	Death - not otherwise specified
Yes	Fatal	Unlikely	Yes	0	Suicide attempt
Yes	Life-threatening	Unlikely	Yes	substitute	Depression
Yes	Life-threatening	Unlikely	Yes	0	Suicidal ideation
Yes	Life-threatening	Unrelated	Yes	0	Depression
Yes	Life-threatening	Unrelated	Yes	substitute	Breast cancer diagnosis
Yes	Life-threatening	Unlikely	Yes	0	Depression
Yes	Life-threatening	Unlikely	No	36	Lung cancer diagnosis and treatment
Yes	Life-threatening	Unlikely	No	substitute	Lung cancer diagnosis and treatment
Yes	Life-threatening	Unrelated	No	36	Appendicitis perforated
Yes	Mild	Unrelated	Yes	8	Hyperlipidemia
Yes	Moderate	Unrelated	Yes&	36	Chest pain - nonspecific
Yes	Moderate	Unrelated	No	substitute	Pain due to car accident
Yes	Moderate	Unrelated	No	0	Worsening pulmonary function (FEV1 value <70%)
Yes	Moderate	Unrelated	No	36	Back pain due to car accident
Yes	Moderate	Unlikely	No	substitute	Non-cardiac chest pain
Yes	Severe	Unrelated	Yes*	8	Appendicitis
Yes	Severe	Unrelated	Yes*	8	Appendicitis perforated
Yes	Severe	Unrelated	Yes*	0	Hyperkalemia
Yes	Severe	Unlikely	Yes*	36	Tracheal narrowing
Yes	Severe	Unrelated	Yes*	36	Fracture
Yes	Severe	Unlikely	Yes*	36	Adrenal insufficiency
Yes	Severe	Unlikely	Yes*	substitute	Fracture
Yes	Severe	Unlikely	Yes&	substitute	Pneumonia
Yes	Severe	Unrelated	Yes&	substitute	Urinary tract infection
Yes	Severe	Unrelated	Yes	8	Stroke
Yes	Severe	Unrelated	Yes	36	Liver cancer diagnosis
Yes	Severe	Unrelated	No	0	Infection
Yes	Severe	Unlikely	No	0	COPD exacerbation
Yes	Severe	Unrelated	No	8	Stomach pain/bleeding
Yes	Severe	Unlikely	No	36	Pneumonia
Yes	Severe	Unrelated	No	substitute	Rheumatoid Arthritis
Yes	Severe	Unlikely	No	8	Upper respiratory infection; asthma attack
Yes	Severe	Unlikely	No	0	Kidney stone and treatment

Yes	Severe	Unlikely	No	36	Bowel obstruction; hernia; hernia treatment; gall bladder removal
Yes	Severe	Unlikely	No	substitute	Diverticulitis; hernia; hernia surgery
Yes	Severe	Unrelated	No	0	Breast cancer diagnosis and treatment
Yes	Severe	Unlikely	No	substitute	Pneumonia
Yes	Severe	Unlikely	No	36	Myocardial infarction; stent replacement
Yes	Severe	Unlikely	No	8	Ovarian torsion; surgery
Yes	Severe	Unlikely	No	36	Heart failure
Yes	Severe	Unrelated	No	substitute	Hiatal hernia
Yes	Severe	Unrelated	No	substitute	Dehydration; kidney disorder
Yes	Severe	Unlikely	No	0	Gastritis
No	Life-threatening	Unrelated	Yes	8	Hyperglycemia
No	Life-threatening	Unrelated	Yes	8	Hyperkalemia
No	Life-threatening	Unrelated	No	substitute	Hypertriglyceridemia
No	Life-threatening	Unrelated	No	36	Hypertriglyceridemia
No	Life-threatening	Unrelated	No	36	Hypertriglyceridemia
No	Life-threatening	Unrelated	No	0	Hypertriglyceridemia
No	Life-threatening	Unlikely	No	36	Hypocalcemia
No	Severe	Unrelated	Yes*	8	Hypertension
No	Severe	Unrelated	Yes*	8	Hypertension
No	Severe	Unlikely	Yes*	36	Hypertension
No	Severe	Unrelated	Yes*	0	Hypertension
No	Severe	Unrelated	Yes*	0	Hypertension
No	Severe	Unrelated	Yes*	substitute	Elective orthopedic surgery
No	Severe	Unrelated	Yes*	0	Hypertriglyceridemia
No	Severe	Probable	Yes*	36	Cough
No	Severe	Unlikely	Yes*	36	Hypertension
No	Severe	Unrelated	Yes*	36	Hypertriglyceridemia
No	Severe	Unrelated	Yes*	8	Hypertriglyceridemia
No	Severe	Unrelated	Yes*	substitute	Hypertriglyceridemia
No	Severe	Unrelated	Yes*	36	Hypertriglyceridemia
No	Severe	Unrelated	Yes&	0	Hypertriglyceridemia
No	Severe	Unrelated	Yes	36	Hypertension
No	Severe	Unlikely	Yes	0	Hypertension
No	Severe	Unlikely	Yes	8	Hypertension
No	Severe	Unrelated	No	0	Tooth infection; treatment
No	Severe	Unrelated	No	8	Hypertension

No	Severe	Unrelated	No	8	Hypertension
No	Severe	Unrelated	No	substitute	Hypertension
No	Severe	Unrelated	No	0	Hypertension
No	Severe	Unlikely	No	0	Hypertension
No	Severe	Unrelated	No	substitute	Hypertension
No	Severe	Unrelated	No	0	Hypertension
No	Severe	Unrelated	No	0	Sinusitis
No	Severe	Unrelated	No	36	Hypertension
No	Severe	Unlikely	No	8	Hypertension
No	Severe	Unlikely	No	0	Hypertension
No	Severe	Unrelated	No	8	Hypertension
No	Severe	Unrelated	No	0	Hypertension
No	Severe	Unrelated	No	0	Hypertension
No	Severe	Unlikely	No	36	Hypertension
No	Severe	Unlikely	No	substitute	Hypertension
No	Severe	Definite	No	8	Dyspnea
No	Severe	Unrelated	No	36	Syncope
No	Severe	Unrelated	No	substitute	Hypertension
No	Severe	Unrelated	No	substitute	Hypertension
No	Severe	Unrelated	No	0	Hypertension
No	Severe	Unlikely	No	0	Hypertension
No	Severe	Unrelated	No	0	Hypertension
No	Severe	Unrelated	No	8	Hypertension
No	Severe	Unrelated	No	36	Hypertension
No	Severe	Unlikely	No	8	Hypertension
No	Severe	Unrelated	No	0	Hypoglycemia
No	Severe	Unrelated	No	substitute	Hypertension
No	Severe	Unrelated	No	substitute	Hypoglycemia
No	Severe	Unlikely	No	substitute	Angioedema
No	Severe	Unlikely	No	0	Depression
No	Severe	Unlikely	No	0	Depression
No	Severe	Unlikely	No	0	Tooth infection; treatment
No	Severe	Unrelated	No	36	Fracture
No	Severe	Unlikely	No	0	Syncope
No	Severe	Unrelated	No	8	Hypertriglyceridemia
No	Severe	Unlikely	No	0	Back pain; treatment
No	Severe	Unlikely	No	8	Hypertriglyceridemia
No	Severe	Unlikely	No	36	Tremor

No	Severe	Possible	No	8	Cough; Syncope
No	Severe	Unlikely	No	36	Hypertension
No	Severe	Unlikely	No	36	Dyspnea
No	Severe	Unlikely	No	36	Hypertension
No	Severe	Unrelated	No	substitute	Hypertension
No	Severe	Unlikely	No	36	Mitral valve disease
No	Severe	Unrelated	No	substitute	Pneumonia
No	Severe	Unlikely	No	substitute	Back pain
No	Severe	Unlikely	No	substitute	Urology-related surgery
No	Severe	Possible	No	0	Hypertension
No	Severe	Unlikely	No	36	Pneumonia
No	Severe	Unlikely	No	36	Back pain

Note: Abbreviations: AE, adverse event; W, week. Multiple symptoms related to the same event in the same participant are only counted once. There are 120 events with 94 participants. Among the 94 participants, 1 participant had 4 events, 2 participants had 3 events, 19 participants had 2 events, and 72 participants had 1 event.

*PI decision to withdraw from study for unrelated reason (i.e., missed three consecutive visits).

&Participant self-withdrew from study.

Complete Statistical Analysis Plan Documentation

Statistical Analysis Plan -

Randomized Controlled Trial Methods for Novel Tobacco Products Evaluation

Version: 4

Authors:

Caroline Cobb

Miao-Shan Yen

Le Kang

Shumei Sun

Thomas Eissenberg

Jonathan Foulds

Date: 11/8/2019

Table of Contents

Section 1: Administrative Information
1.1. Title

Randomized Controlled Trial Methods for Novel Tobacco Products Evaluation

1.2. Trial Registration

ClinicalTrials.gov Identifier: NCT02342795

1.3. SAP version

SAP Version 3

1.4. Protocol version

Amendment 19 – Version Date: 1/1/2018

1.5. SAP Revisions

1.5.1. SAP revision history

- Version 1 – approved 12/1/2014
- Version 2 – approved 8/3/2018
- Version 3 – approved 12/14/2018
- Version 4 – approved 11/08/2019

1.5.2. SAP revision justification

- Version 1 – Original statistical analysis plan and power justification published in the Lopez et al., 2016 and included in the primary site protocol originally approved by the VCU IRB.
- Version 2 – Expanded and amended statistical analysis plan to be more comprehensive in the description of the primary, secondary, and exploratory outcomes and their associated analyses, also included relevant information based on other statistical analysis plan source documents (Gamble et al., 2017; CENIC 2: Project 2 SAP, Version-4/12/2018 provided by E. Donny; Statistical analysis plan sample template for clinical trial disclosure projects, no date available available at: https://www.pfizer.com/files/research/research_clinical_trials/Clinical_Data_Access_Request_Sample_SAP.pdf).
- Version 3 – Added detail regarding the definition of cigarette smoking abstinence under exploratory outcomes to be more specific/empirically-based; clarified the approach to missing data for exploratory outcomes considering the resources for multiple imputation models may not be feasible for all study team members/manuscript teams.
- Version 4 – Edited the primary analysis description (“two-way ANOVA with repeated measures”) to be consistent with secondary analyses described (linear mixed models) as well as sensitivity models/analyses (several of which are not best suited to a standard ANOVA model), comparison of findings across primary/secondary/sensitivity models is critical to their interpretation; removed specification that urinary NNAL and cotinine would be examined with and without adjustment for creatinine concentration (retained adjustment with creatinine concentration as this is the most common among the relevant literature).

1.5.3. Timing of SAP revision in relation to interim analyses

- Not applicable; no interim analyses

1.6. Roles and Responsibility

- Caroline Cobb, PhD[a], drafted and reviewed the SAP
- Miao-Shan Yen, MS[b], drafted and reviewed the SAP
- Le Kang, PhD[b], drafted and reviewed the SAP
- Shumei Sun, PhD[b], advised and reviewed the SAP
- Thomas Eissenberg, PhD[a], advised and reviewed the SAP
- Jonathan Foulds, PhD[c], advised and reviewed the SAP

a. Virginia Commonwealth University, Center for the Study of Tobacco Products, Richmond, VA

b. Virginia Commonwealth University, Department of Biostatistics, Richmond, VA

c. Penn State University Department of Public Health Sciences, Tobacco Center of Regulatory Science, College of Medicine, Hershey, PA

1.7. Approvals and Date

Caroline Cobb – 11/08/2019 (via email)

Miao-Shan Yen - 11/07/2019 (via email)

Le Kang - 11/07/2019 (via email)

Shumei Sun - 11/07/2019 (via email)

Thomas Eissenberg - 11/07/2019 (via email)

Jonathan Foulds - 11/07/2019 (via email)

Section 2: Introduction
2.1. Background and rationale

The tobacco marketplace in the U.S. is changing fast, while regulatory science lags behind. The FDA can alter this dynamic, but needs the tools to do so. One necessary tool is a model for evaluation of all types of "modified risk tobacco products" (MRTPs): novel products marketed with the claim that they reduce harm or risk associated with the use of conventional products. Such claims need to be evaluated and the products regulated accordingly. However, few models have been proposed for this purpose. This project will show how Randomized Controlled Trial (RCT) methods can inform pre-market evaluation by examining the influence of real world product use on biomarkers of toxicant exposure and disease risk, reports of adverse events, and concurrent use of other tobacco products. Electronic cigarettes (ECIGs) are the focus product for this study. Overall, this project will demonstrate how regulatory science is advanced by an integrated, iterative model of MRTP evaluation that includes RCT methods.

2.2. Objectives

The specific aims of the RCT are to:

1) *Characterize product influence on toxicants, biomarkers, health indicators, and disease risk*. We will measure exposure to the carcinogenic nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK; via its metabolite NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) in urine], expired air carbon monoxide (CO), and nicotine (via its metabolite cotinine in urine). We will also measure heart rate and blood pressure, biochemical and hematologic health indices, pulmonary function (via spirometry), and biomarkers of oxidative stress. With respect to toxicant exposure, we hypothesize that, relative to the cigarette substitute condition, we will observe ECIG liquid nicotine concentration-related decreases in urine NNAL and expired air CO concentration.

2) *Determine the tobacco abstinence symptom and adverse event profile associated with real-world product use*. We will use standard measures of nicotine/tobacco abstinence symptoms (i.e., MNWS, Questionnaire of Smoking Urges) to characterize the extent to which ECIG-induced suppression of abstinence symptoms is related to nicotine concentration. With respect to other adverse events, we will assess effects likely attributable to inhalation of propylene glycol and nicotine self-administration. We hypothesize more of these propylene glycol-related adverse events with ECIGs relative to the cigarette substitute condition.

3) *Examine the influence of novel product use on conventional tobacco product use.* We will monitor ECIG and all other tobacco/nicotine product use closely, via daily tobacco use diaries and in-person assessments. Because we are targeting individuals interested in reducing their cigarette intake, we hypothesize ECIG nicotine concentration-related reductions in combustible cigarette use.

Section 3: Study Methods
3.1. Trial Design

The study is a two-site, four-arm, 6-month, parallel-group randomized controlled trial with a follow-up to 9 months.

3.2. Randomization

Blocked randomization was accomplished with a 1:1:1:1 ratio of condition assignments at each participating institution with the original goal of 260 randomized at each site totaling 520. Based on slower recruitment at the VCU site, this randomization allocation by site was changed (10/5/2015) with VCU randomizing 200 and PSU randomizing 320 (totaling 520). The assignment codes were made from separate randomization lists created in advance by the statistician for each site stratum.

3.3. Sample Size

RCT power was based on the important biomarker of toxicant exposure, NNAL concentration in urine. Unfortunately, there were no data that revealed the NNK exposure in ECIG users, as that study has not yet been performed. However, we do have data showing how NNAL concentration in novel tobacco product users compared to own brand cigarette use (Breland, Kleykamp, & Eissenberg, 2006). Using these data, power analysis revealed 100 completers per condition would provide an 80% power to detect an effect size of 58.59 pg/mL (SD = 125.55 pg/mL) on NNAL. We aimed to enroll 130 participants per condition (across sites) anticipating a 20% attrition rate.

3.4. Framework

3.4.1. Randomized assignment to one of four conditions (cigarette substitute; ECIG with 0 mg/ml nicotine liquid; ECIG with 8 mg/ml nicotine liquid; ECIG with 36 mg/ml nicotine liquid; ECIG nicotine dose administered double-blind).

3.4.2. Primary outcome hypothesis is that relative to the cigarette substitute there will be nicotine dose related decreases in total NNAL.

3.5. Statistical interim analyses and stopping guidance

3.5.1. No interim analyses regarding the primary or secondary outcomes were planned or carried out.

3.5.2. There are no planned adjustments based on interim analyses.

3.5.3. Stopping Rules

3.5.3.1. The Data and Safety Monitor Board (DSMB) is comprised of four scientists not otherwise affiliated with the clinical trial (please see DSMP/DSMB documentation for more information). The DSMB reserves the right to discontinue or suspend the study at any time, at an individual site or overall, for safety or for administrative reasons. In the event of such action, the DSMB will promptly inform the impacted Investigators and institutions, the regulatory authorities, and the Institutional Review Board (IRB) of the action and the reason(s) for the action.

3.5.3.2. Medical Monitors

The roles of the Medical Monitors are to:

- Review and provide definitive adjudication on individual adverse events (AE).
- Make specific recommendations for study product dispensing.

3.5.3.3. Recording and Definition of Adverse Events (per VCU Protocol_A19_1.1.)

Adverse events are recorded and reviewed for updates/changes at every study visit following Visit 1 as well as documented if a participant makes a report via phone or email.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study device will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy. **Note:** Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study.
- The test finding is considered an adverse event by the investigator.

Table 3-1. Adverse Event Definitions

Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than “adverse reaction”. • *Reasonable possibility.* For the purpose of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected	An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND

suspected adverse reaction.	application; or is not listed at the specificity or severity that has been previously observed and/or specified.
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

3.5.3.4 Safety monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **research coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

Table 3-2. Definitions of Adverse Event Class

Class	Severity	Expectedness/Relatedness	Location	Reporting Timeline
1	Serious	- Unexpected - Related or possibly related	All	2 business days from occurrence
2	Non-serious	- Unexpected - Related or possibly related	All	Annual
3	Serious or non-serious	- Expected	All	Annual

3.6. Timing of outcome assessments

Time points at which each of the primary, secondary, and other/exploratory outcomes are measured including visit "windows" are listed below.

Table 3-3. Timing of Assessments and Study Windows

	Before Consent	Consent	Reduction Phase				Continuation Phase					Follow-Up Phase	
			Baseline										
Study Visit	**NA**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Study Week	**NA**	**-1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**36**
Days	**NA**	**-7**	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**197**	**253**
Study Visit Window	**NA**	**-7**	**-1/ +3**	**-3/ +3**	**-3/ +7**	**-7/ +14**	**-7/ +14**	**-7/ +14**	**-7/ +14**	**-7/ +14**	**-7/ +42**	**-7/ +14**	**-7/ +14**
Participant Instructions:													
Smoke normally for one week		**x**											
Randomize participants			**x**										

Reduce cigarette consumption by 50%			x	x									
Reduce cigarette consumption by 75%					x	x							
Continue to reduce cigarette consumption							x	x	x	x			
Cease all combustible tobacco use											x		
Baseline Measurements:													
Demographics		x											
Tobacco Use History		x											
Treatment History		x											
Cigarette Details		x	x										
Medical History		x											
Concomitant Medications		x	x	x	x	x	x	x	x	x	x	x	x
Drug/Alcohol Measures:													
Alcohol AUDIT-C		x				x					x		x
NIDA Quick Screen		x						x			x		x
Adverse events:													
AE Trigger Question			x	x	x	x	x	x	x	x	x	x	x
AE Log			x	x	x	x	x	x	x	x	x	x	x
Cigarette Measures:													
MNWS			x	x	x	x	x	x	x	x	x	x	x
Confidence to Quit											x	x	x
Stage of Change											x	x	x
Environmental Smoke			x								x		x
Smoking Urges			x	x	x	x	x	x	x	x	x	x	x
7-day TLFB & Current Tobacco Use			x	x	x	x	x	x	x	x	x	x	x
Cigarette Dependence													
Cigarette Dependence			x	x	x	x	x	x	x	x	x	x	x
Study Product Dependence													

E-Cigarette Dependence Scale (if product = ecig)				x	x	x	x	x	x	x	x	x	x
Non-Study E-Cigarette Dependence Scale				x	x	x	x	x	x	x	x	x	x
Cig Substitute Dependence Scale (if product = cig sub)				x	x	x	x	x	x	x	x	x	x
E-Cigarette Patterns of Use (if product = ecig)				x	x	x	x	x	x	x	x	x	x
Study Product Measures:													
Study Product Side Effects				x	x	x	x	x	x	x	x	x	x
Study Product Evaluation				x	x	x	x	x	x	x	x	x	x
Study Product Trigger				x	x	x	x	x	x	x	x	x	x
Study Product Dispensed Log			x	x	x	x	x	x	x	x	x		
Psych Measures:													
Kessler 6			x			x	x		x		x		x
Perceived Stress			x			x	x		x		x		x
CES-D			x			x	x		x		x		x
Health Measures:													
Interheart			x								x		x
Clinical COPD Questionnaire			x								x		x
Biomeasures:													
Pulmonary Function Test			x			x		x			x		x
CO		x	x	x	x	x	x	x	x	x	x	x	x
Waist/Hip Ratio			x								x		x
Vitals (HR/BP)		x	x	x	x	x	x	x	x	x	x	x	x
Height			x										
Weight			x	x	x	x	x	x	x	x	x	x	x
Exhaled Breath Condensate Samples:			x			x		x			x		
Oxidative Stress - 8 Isoprostanes & other biomarkers			x			x		x			x		
Blood Samples:													
Complete Metabolic Panel			x								x		

Hematology Panel			x								x		
Lipid Panel			x								x		
C-Reactive Protein			x								x		
Oxidative Stress - Glutathione			x			x		x			x		
Urine Samples:													
Pregnancy Test		x											
Cotinine			x			x		x			x		
NNAL			x			x		x			x		
Oxidative Stress - 8 Isoprostanes & 8-OHdG			x			x		x			x		
Other:													
Screener 1	x												
Screener 2	x												
Screener 3		x											
End of trial form													X

Section 4: Statistical Principles

4.1. Level of statistical significance and adjustment for multiplicity

All statistical tests will be two-sided. The allowed type I error rate is set at 0.05. P-values less than 0.05 will be considered statistically significant, with the exception of the post-hoc analysis of primary outcome between any two research interventions, where p-values less than 0.008 will be considered significant based on Bonferroni corrections for multiple comparison adjustment.

All analyses will be completed using the intent-to-treat (ITT) approach to avoid the bias associated with the non-random loss of participants for the real life intervention effect.

Per-protocol (PP) analysis will also be conducted for the participants who adhered to the study protocol (attended and provided data at Visits 2, 5, 7, and 10) to estimate the true efficacy. Methods for handling missing data will be specified below.

4.2. Confidence intervals to be reported

A 95% Confidence Interval will be reported when appropriate.

4.3. Protocol deviations

4.3.1. Definition of protocol deviations and violations for the trial

Protocol deviations are situations where activities of the study diverge from the IRB approved study protocol. They may be accidental or unintentional changes to, or non-compliance with the study protocol that does not increase the risk or decrease the benefit to the participant. It also does not have an effect on the participant's rights, safety, welfare and/or integrity of the data. Deviations may result from the action of the subject, researcher or research staff.

Protocol deviations may not be reportable to the IRB but should be documented in REDCap on the Protocol Deviations Violations form.

The following will be considered Protocol Deviations throughout the study:

- **Training:**
  - Study staff who has not been fully trained on study procedures completes visits
- **Researcher oversight:**
  - Study visit offered to a participant that is outside a study window (this does not include a rescheduled visit that is scheduled outside the window due to a conflict in the participant's schedule)
  - Failure on the part of the researcher to collect subject data or specimens (this does not include incidents that are out of the researchers control, i.e. a participant refuses or leaves unexpectedly)

    - Failure to give participants study visit payment
- **Blood/urine samples:**
    - Pregnancy test was not performed on visit dates where required
    - Blood or urine was collected but not documented in REDCap or the specimen logs
    - Blood was not processed and frozen within the 2 hour time window
    - Blood samples were improperly labeled, logged, and/or packaged when shipped but did not result in lost or unidentifiable samples
- **Clinic procedures:**
    - Incorrect information was entered into spirometry software yielding incorrect predicted values
- **Participants:**
    - Subject refuses to complete research activities that they have otherwise consented to (questionnaires, blood/urine collection etc.)
- **Confidentiality:**
    - Inclusion of identifying information on sample shipments
- **Study Product:**
    - Cartomizers given to participant after expiration date

Protocol violations are more serious and may reduce the quality or completeness of the data, make the informed consent inaccurate or impact the participant's safety, rights or welfare.

Protocol violations **are reportable to the PSU IRB** and if they result in an **unanticipated problem are reportable to the VCU IRB**.

The following will be considered protocol violations throughout the trial:

- **Confidentiality:**
    - Breaches of confidentiality resulting from lost, misplaced, or stolen study documents (e.g., a consent form is missing)
    - Inclusion of identifying information on sample shipments
- **Consent form:**
    - Failure to obtain valid informed consent prior to any study-specific tests/procedures
    - Missing signature or date from either participant or researcher
    - Outdated or incorrect consent form used
- **Randomization:**
    - A participant is consented into the study who does not meet initial inclusion/exclusion criteria
    - Participant is entered into randomization phase prior to determining final compliance criteria
- **IRB:**
    - Unreported SAEs to the IRB within 5 days
    - Approvals not current, suspended or terminated
    - Enrollment occurs during a period when study is "on hold"
    - Enrollment over the IRB approved enrollment total
- **Tests/Samples:**
    - Incorrect or missing tests (PFT, blood, EBC or urine samples) that were documented as complete
    - Mishandled samples: Blood, urine, or EBC samples were not labeled, logged, and/or packaged properly when shipped resulting in lost samples
- **Safety:**
    - Participant was allowed to continue with the study after a positive pregnancy test
    - Participant was given study product when withdrawal criteria was met
    - Participant was allowed to continue with the study after any other hard withdrawal criteria are met
- **Participants:**
    - Visits are repeatedly scheduled outside study windows
- **Data Collection:**
    - Phone and/or survey contacts were not attempted as scheduled due to researcher oversight

4.3.2. Description of which protocol deviations will be summarized

Percentages of protocol deviations related to research oversight, blood/urine samples, clinic procedures, and study products will be summarized by site and by conditions.

4.4. Analysis populations

4.4.1. The primary analysis of all endpoints will adhere to the ITT principle, while PP analysis will also be considered to provide additional insights about true efficacy. Under the ITT principle, all randomized subjects will be included in the analysis in the group to which they were randomized, regardless of protocol violations and compliance to treatment assignment; while the PP analysis will be restricted to those participants who adhered to the study protocol.

4.4.2. Subgroup populations

None are planned.

Section 5: Trial Population
5.1. Screening Data and Eligibility

Participant screening data (collected via phone via a pre-screener and in-person at Visit 1) will be reported for all items related to primary inclusion and exclusion criteria. Inclusion and exclusion eligibility criteria are described below.

Inclusion Criteria

- Age 21-65
- Smoke >9 cigarettes per day for at least 1 year
- Smoke regular filtered cigarettes or machine-rolled cigarettes with a filter
- CO measurement >9 ppm at baseline
- No serious quit attempt in the prior 1 month. This includes use of any FDA approved smoking cessation medication (varenicline, bupropion [used specifically as a quitting aid], patch, gum, lozenge, inhaler, and nasal spray) in the past 1 month as an indication of treatment seeking.
- Not planning to quit in the next 6 months
- Interested in reducing cigarette consumption
- Willing to attend visits weekly and monthly over a 9-month period (not planning to move, not planning extended vacation, no planned surgeries
- Read and write in English
- Able to understand and consent

Exclusion Criteria

- Pregnant and/or nursing women
- Unstable or significant medical condition in the past 12 months (Recent heart attack or some other heart conditions, stroke, severe angina including high blood pressure if systolic >159 or diastolic >99 observed during screening).
- Severe immune system disorders (uncontrolled HIV/AIDS; unstable multiple sclerosis symptoms), respiratory diseases (exacerbations of asthma or COPD, require oxygen, require oral prednisone), kidney (dialysis) or liver diseases (cirrhosis), or any medical disorder/medication that may affect participant safety or biomarker data.
- Use of any non-cigarette nicotine delivery product (pipe, cigar, dip, chew, snus, hookah, ECIGs, strips, sticks) in the past 7 days
- Uncontrolled mental illness or substance abuse or inpatient treatment for these in the past 6 months
- History of difficulty providing or unwilling to provide blood samples (fainting, poor veins, anxiety)
- Surgery requiring general anesthesia in the past 6 weeks
- Use of an ECIG for 5 or more days in the past 28 days or any use in the past 7 days
- Use of marijuana or any illicit drug/prescription drugs for non-medical use daily/almost daily or weekly in the past 3 months per NIDA Quick Screen
- Use of hand-rolled, roll your own cigarettes
- Known allergy to propylene glycol or vegetable glycerin
- Other member of household participated in the study

5.2. Recruitment

The CONSORT flow diagram for the study will include the proportion of the sample assessed for eligibility via the pre-screener, eligible/ineligible for Visit 1, attended/excluded/eligible at Visit 1, attended/excluded/randomized at Visit 2, study condition/arm assigned at Visit 2, and for Visits 3-12 attended/no-show/withdrawn (reason for withdrawal) by study condition/arm assigned.

5.3. Withdrawal/follow-up

Withdrawal from the study will be defined using the end of trial form (PI decision, participant decision to withdraw, withdrawal for serious adverse event). Sub-categories for each type of withdrawal will be presented by study condition assigned and by site.

5.4. Baseline participant characteristics

Baseline characteristics to be summarized include demographics (age, sex, race, ethnicity, education, employment status, total household income, marital status), tobacco use characteristics (average cigarettes smoked per day, years smoking, age of cigarette smoking initiation, ever use of other tobacco products, menthol status, PSU Cigarette Dependence Scale score, Visit 2 average cigarettes per day), and psychosocial/health characteristics (AUDIT score, Environmental Smoke Score, Kessler K6 Score, Perceived Stress Score, CES-D Score, Interheart Score, Clinical COPD Score), physiological measures (waist circum, hip circum, heath, weight, BMI, BP, Pulse, FEV1, FVC, urine cotinine, urine NNAL, and expired air CO).

Section 6: Analysis
6.1. Outcome definitions and timing

- Primary outcome: The primary outcome measure of this RCT is the urinary concentration of the carcinogen biomarker of tobacco exposure, total NNAL (linear range: 20 to 20,000 pg/mL or 0.020 to 20 ng/mL. Results will be presented adjusted for creatinine

concentration (pg/ng per mg creatinine). This outcome is measured at Visit 2 (Week 0), Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10 (Week 24).

- Secondary outcomes:
  o Cotinine concentration will be measured via urine sample (linear range: 1000 to 3,000,000 pg/mL or ng/mL or 1-3000 ng/mL). Results will be presented adjusted for creatinine concentration (pg/ng per mg creatinine). This outcome is measured at Visit 2 (Week 0), Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10 (Week 24).
  o Total glutathione will be measured via blood sample (linear range information unavailable). This outcome is measured at Visit 2 (Week 0), Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10 (Week 24).
  o 8-Isoprostanes will be measured via urine sample (linear range information unavailable). Results will be presented unadjusted and adjusted for creatinine concentration (pg/ng per mg creatinine. This outcome is measured at Visit 2 (Week 0), Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10 (Week 24).
  o 8-Isoprostanes will be measured via exhaled breath condensate sample (linear range information unavailable). This outcome is measured at Visit 2 (Week 0), Visit 5 (Week 4), Visit 7 (Week 12), and Visit 10 (Week 24).

- Exploratory outcomes (timing varies between Visit 1-12):
  - From Aim 1
    - Exhaled CO
    - Heart rate/blood pressure
    - Spirometry outcomes
    - 8-OHdG in urine samples
    - Other oxidative stress markers in exhaled breath condensate samples.
    - Blood lab results
  - From Aim 2
    - Adverse events profile
      - By overall frequency, by relatedness category, severity, and by system affected
    - Study Product Side Effects
    - Study Product Evaluation
    - Minnesota Nicotine Withdrawal Scale (MNWS)
    - Questionnaire of Smoking Urges
  - From Aim 3
    - 7-day TLFB form
      - Cigarettes smoked per day (7-day average)
      - Study product use per day (7-day average)
      - Study product cartomizers dispensed/used returned
      - 50% reduction in cigarettes smoked (defined as 50% reduction of Visit 1 self-reported CPD; yes/no)
      - 75% reduction in cigarettes smoked (defined as 50% reduction of Visit 1 self-reported CPD; yes/no)
      - Study product abstinence
        - 24-hour use (available at Visits 3-12; yes/no)
      - Cigarette smoking abstinence (defined as 0 cigarettes smoked via 7-day average and expired air CO <10 at the same visit; SRNT Subcommittee, 2002)
        - 24-hour point prevalence cigarette smoking abstinence (available at Visits 3-12; yes/no)
        - 7-day point prevalence cigarette smoking abstinence (available at Visits 3-12; yes/no)
        - 28-day point prevalence cigarette smoking abstinence (available at Visits 6-11; yes/no)
      - Other tobacco use
        - For each product reported 7-day average
        - Summary across products 7-day average
    - Cigarette Dependence Scale
    - Non-Study E-Cigarette Dependence Scale
    - Cigarette Substitute Dependence Scale
    - E-Cigarette Dependence Scale
    - E-Cigarette Patterns of Use
    - Study Product Dispensed Log
  - Other outcomes
    - AUDIT-C
    - CES-D
    - Clinical COPD Questionnaire
    - Perceived Stress
    - Kessler K6
    - Interheart
    - Environmental Smoke Questionnaire

6.1.2. Any calculation or transformation used to derive the primary and secondary outcomes (i.e., change from baseline)

None planned other than corrected/non-corrected values for creatinine where applicable and potential transformation for outcomes that do not meet model assumptions such as normality.

6.1.3. Any calculation or transformation used to derive the exploratory outcomes (i.e., change from baseline)

Changes from baseline may be calculated for some exploratory analyses as needed. Sum scores of MPSS, FTND, PSCDI, HONC, AUDIT-C, MNWS-R, Perceived Stress, Kessler 6, CES-D, Interheart and Clinical COPD will be calculated. Level of exposure to environmental smoke will be categorized based on the responses from the environmental smoke questionnaire. Averages of 7-CPD/study product use will be calculated based on the 7-day TLFB form (please note days that overlap in the 7-day TLFB will be dropped from the more recent visit).

6.2. Analysis methods

6.2.1. Primary and Secondary Analyses

We will first examine baseline demographics described above to identify any baseline imbalances after randomization. Discrete variables will be summarized by frequencies with percentages and compared using Chi-squared test or Fisher's exact test when appropriate. Continuous covariates will be summarized by mean with standard deviation, or median with range, and compared using one-way ANOVA or Kruskal-Wallis test. We expect groups to be balanced for important baseline demographics due to the nature of RCT.

Our primary endpoint, urine NNAL concentration, will be summarized by study intervention and timepoint and analyzed using linear mixed models (between-subjects factor: study condition/arm; within-subjects factor: visit, 2, 5, 7, 10), and we will adjust the type I error rate to account for 6 pairwise comparisons between study conditions/arms over time, and at each time point. We will compare each ECIG group to the cigarette substitute and then each ECIG group to the other. An analogous approach will be used to analyze our secondary endpoints. The analyses of our secondary endpoints will primarily use one-way ANOVA at different timepoint with similar multiple comparison adjustments.

Secondary data analyses will consist of adjusted analyses including age, gender, race, and possibly for other covariate imbalance (including by site) with the use of linear mixed models.

6.2.2. Any adjustment for covariates

A secondary analysis (as described above) will be completed adjusting for age, gender, race, along with any other covariates that significantly differ across study conditions at baseline, or any other covariates particularly relevant to the primary/secondary outcomes. A stepwise model selection will be performed to finalize the list of covariates to be included in the final model.

6.2.3. Methods used for assumptions to be checked for statistical methods

Data normality will be confirmed by using graphical methods including quantile-quantile plot (QQ plot) and Kolmogorov-Smirnov test.

6.2.4. Details of alternative methods to be used if distributional assumptions do not hold

Skewed continuous variables will be log-transformed or Box-Cox transformed as appropriate.

6.3. Safety

The distinction between the primary/secondary outcomes and safety outcomes is not as clear in this trial as it would be in a typical clinical trial of a novel therapeutic agent. Many outcomes that would typically be considered potential adverse consequences or safety outcomes will be analyzed as the secondary or exploratory outcomes as described above.

AEs and SAEs will be recorded as described in the Adverse Event SOP. AEs will be tabulated and compared across treatment groups in the exploratory analyses. We expect study product-related SAEs to be rare and, therefore, no formal statistical comparison for this AE category is planned for this trial.

6.4. Missing data

An ITT analysis includes subjects that are allocated according to their random intervention assignment, regardless of compliance to the study product, and that complete data are available on all study subjects. Every effort will be made to limit the amount of missing data in this trial. Study participants will be incentivized to attend study sessions and provide biological samples and other measurements as detailed in the study protocol. However, some level of missing data is inevitable in a study of this kind. In response, we will complete a sensitivity analysis for the primary and secondary endpoints in order to evaluate the robustness of our conclusions to missing data.

We will compare subjects with and without missing primary outcome data in order to identify baseline covariates associated with missing data. There are three possible scenarios of missing data in our study: (1) primary outcome measurements missing while covariate measurements completely available, (2) primary outcome measurements available but some measurements in covariates missing, and (3) both primary outcome and some covariate measurements missing. Our primary approach to handling missing data in scenario 1 and 2 will be multiple imputation where missing values are imputed using conditional regression models developed from baseline covariates (Little & Rubin, 2002) and/or available outcomes. Our strategy to handle missing data in scenario 3 is multiple imputation through joint conditional specification (Schafer, 1997).

In addition, we will conduct a series of sensitivity analyses of the primary and secondary endpoints using baseline-carried-forward and last-observation carried forward. The results of these analyses will be compared to the primary analysis to evaluate the robustness of our conclusions.

Note that we intent to examine the potential differential dropout or attrition between interventions and study sites. If there is information suggesting data missing are not at random, e.g., the dropout rates are evidently different between interventions or sites, multiple imputation model equations should not incorporate intervention or site variable. Alternatively, multiple imputation may be carried out one intervention at a time, or one site at a time, respectively (Li, Stuart, & Allison, 2015).

6.5. Additional analyses

Exploratory endpoints will be analyzed following a similar approach to what has been proposed for the primary and secondary endpoints. Continuous and binary endpoints will be analyzed using an ANOVA, linear regression, or logistic regression, respectively, and secondary data analyses will be performed using linear mixed models or generalized linear mixed models, as appropriate. Skewed continuous endpoints will be log-transformed and analyzed on the log-scale for analysis. Time-to-event endpoints will be analyzed using Cox proportional hazards model. The primary analysis of all endpoints will be without adjustment for baseline covariates.

The secondary analysis will be completed adjusting for age, gender, and race, along with any other covariates that differ significantly across study conditions at baseline, or any other covariates particularly relevant to the exploratory outcomes (including by site). A stepwise model selection will be performed to finalize the covariates to be included in the final model.

Handling of missing data for exploratory endpoints may or may not utilize multiple imputation (as described for the primary and secondary endpoints), but all exploratory endpoint analyses will include sensitivity checks to examine the robustness of the conclusions drawn with respect to the effects of missing data.

More specific exploratory analyses include:

1) An exploratory analysis of the primary, secondary, and exploratory endpoints will involve recoding of the study condition assignment into a three-level variable: cigarette substitute s. ECIG+0 mg/ml nicotine vs. ECIG+8/36 mg/ml nicotine (i.e., the two nicotine containing conditions will be collapsed).

2) An exploratory analysis of the primary, secondary, and exploratory endpoints will involve adding the use of other tobacco products (combustible/non-combustible) as a covariate (assessed at each study visit).

3) An exploratory analysis of the primary, secondary, and exploratory endpoints will involve adding the current cigarette smoking and/or cigarette dependence scale score as a covariate (assessed at each study visit).

4) An exploratory analysis of the primary, secondary, and exploratory endpoints by site (VCU vs. PSU) due to anticipated demographic heterogeneity in the population recruited.

5) An exploratory analysis of the primary, secondary, and exploratory endpoints by study product adherence status (i.e., use of study product at subsequent visits following randomization).

6.6. Statistical software

All analysis will be completed using SAS (v.9.4).

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Appendix
SAP – Version 1

Randomized Control Trial Methods for Novel Tobacco Product Evaluations

Statistical Analysis Plan

Version 1

Per the Lopez et al. BMC Public Health (2016) 16:217 DOI 10.1186/s12889-016-2792-8

Aim
The specific aims of the RCT are to:

1. Characterize ECIG influence on toxicants, biomarkers, health indicators, and disease risk. We will measure exposure to the carcinogenic nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK; via its metabolite NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) in urine], expired air carbon monoxide (CO), and nicotine (via its metabolite cotinine in urine). We will also measure heart rate and blood pressure, biochemical and hematologic health indices, pulmonary function (via spirometry), and biomarkers of oxidative stress. With respect to toxicant exposure, we hypothesize that, relative to the cigarette substitute condition, we will observe ECIG liquid nicotine concentration-related decreases in urine NNAL and expired air CO concentration.
2. Determine the tobacco abstinence symptom and adverse event profile associated with real-world ECIG use. We will use standard measures of nicotine/ tobacco abstinence symptoms to characterize the extent to which ECIG-induced suppression of abstinence symptoms is related to nicotine concentration. With respect to other adverse events, we will assess effects likely attributable to inhalation of propylene glycol and nicotine self administration.
3. We hypothesize more of these propylene glycol-related adverse events with ECIGs relative to the cigarette substitute condition. Examine the influence of ECIG use on conventional tobacco product use. We will monitor ECIG and all other tobacco/nicotine product use closely, via daily tobacco use diaries and in-person assessments. Because we are targeting individuals interested in reducing their cigarette intake, we hypothesize that individuals randomized to higher ECIG nicotine concentrations (8 mg/ml or 36 mg/ml) will experience reductions in combustible cigarette use.

Primary outcome
The primary outcome measure of this RCT is the urinary concentration of the carcinogen biomarker of tobacco exposure, NNAL.

Secondary outcomes
The secondary outcome measure will be urine cotinine concentration. Markers of oxidative stress (Glutithione and 8-Isoprostanes) are additional secondary outcome measures. Glutathione will be measured via blood sample analysis. 8-Isoprostanes will be measured via both urine sample and exhaled breath condensate analyses.

Sample size
RCT power is based on the important biomarker of toxicant exposure, NNAL concentration in urine. Unfortunately, there are no data that reveal the NNK exposure in ECIG users, as that study has not yet been performed. However, we do have data showing how NNAL concentration in novel tobacco product users compares to own brand cigarette use [49]. Using these data, power analysis revealed 100 completers per condition would provide an 80 % power to detect an effect size of 0.28 pmol/ml (SD = 0.6 pmol/ml) on NNAL. We aim to enroll 130 participants per condition anticipating a 20 % attrition rate.

Statistical analysis
The analysis plan is based on the primary objective of determining the extent to which ECIG nicotine concentration influences NNK exposure as indexed by urinary NNAL concentration. We will first examine baseline characteristics including demographics and smoking history across study interventions to identify any baseline imbalances after randomization. Discrete variables will be summarized by frequencies and percentages and compared using Chisquared test or Fisher's exact test. Continuous covariates will be summarized by mean, standard deviation, median and range, and compared by one-way ANOVA. Skewed continuous variables will be log-transformed or square root transformed as appropriate. We expect groups to be balanced for important baseline characteristics due to randomization.

A secondary analysis will be completed adjusting for age, gender, and race, along with any other covariates that differ across research interventions at baseline with a p-value less than 0.20. P-values less than 0.05 will be considered statistically significant with the exception of analysis of our primary analysis, where p-values less than 0.008 will be considered significant after a Bonferroni multiple comparisons adjustment.

Our primary endpoint, urine NNAL concentration, will be summarized by study intervention and time and analyzed using linear regression, and we will adjust the Type I error rate to account for 6 pairwise comparisons at each time point. We will compare each ECIG group to the cigarette substitute and then each ECIG group to the other. An analogous approach will be used to analyze our secondary endpoints. The primary analysis of our secondary endpoints will use linear regression.

Secondary analyses will consist of an adjusted analysis and a repeated measures analysis using a linear mixed model. All analysis will be completed using SAS (v.9.4) under the expertise of a senior biostatistician.

PER VCU approved protocol (dated 10/29/2014; approved by IRB 12/01/2014)

Statistical Plan

7.0 Sample size determination

We chose to power our RCT based on the important biomarker of toxicant exposure, NNAL concentration in urine. Unfortunately, there are no data that reveal the NNK exposure in electronic cigarette users, as that study has not yet been performed. However, we do have data showing how NNAL concentration in novel tobacco users compares to own brand use. Using these data, and the knowledge that we would be conducting two sample t-tests at the .008 level to control for 6 pairwise comparisons we worked with the biostatistics team to conduct a power analysis. That analysis revealed that 100 completers per condition would provide an 80% power to detect an effect size of .28. We have chosen therefore to enroll 130 participants in each condition, in anticipation of a ~20% attrition rate (Note: We will limit attrition by replacing participants before randomization).

7.1 Statistical methods

Our analysis plan is based on the primary objective of determining the extent to which ECIG dose influences NNK exposure as indexed by urine NNAL level. We will first examine baseline characteristics including demographics and smoking history across research interventions to identify any baseline imbalances after randomization. Discrete variables will be summarized by frequencies and percentages and compared using Chi-squared test of Fisher's exact test. Continuous covariates will be summarized by mean, standard deviation, median and range, and compared by one-way ANOVA. Skewed continuous variables will be log-transformed or square root transformed as appropriate. We expect groups to be balanced for important baseline characteristics due to randomization. A secondary analysis will be completed adjusting for age, gender, and race, along with any other covariates that differ across research interventions at baseline with a p-value less than .20. P-values less than .05 will be considered statistically significant with the exception of analysis of our primary analysis, where p-values less than .008 will be considered significant after a Bonferroni multiple comparisons adjustment. Our primary endpoint, urine NNAL level, will be summarized by research intervention and time and analyzed using linear regression and we will adjust the Type 1 error rate to account for 6 pairwise comparisons at each time point. We will compare each electronic cigarette group to the control and then each electronic cigarette group to the other. An analogous approach will be used to analyze our secondary endpoints. The primary analysis of our secondary endpoints will use linear regression. Secondary analyses will consist of an adjusted analysis and a repeated measures analysis using a linear mixed model. All analysis will be completed using SAS (v.9.3).

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