Supplementary Online Content

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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

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Abbreviations

AE: Adverse event
BP: Blood pressure
BPM: Beats per minute
CEMA: 2-cyanoethylmercapturic acid, biomarker for exposure to acrylonitrile
CESD: Centers for Epidemiological Studies Depression scale; CES-D is designed to measure depressive symptomatology in the general population and is an abbreviated 20 item scale with scores of 0= rarely or none of the time; 1= Some or little of the time; 2= Occasionally or moderate amount of time; 4= Most or all of the time.[1] The range is 0-60 with scores of 16 to 26 indicative of mild depression and scores of 27 or more indicative of major depression.[2,3]
CO: Carbon monoxide; $\geq$ 6 ppm indicative of smoker[4]
COPD: Chronic obstructive pulmonary disease
CPD: Cigarettes per day
FDA: Food and Drug Administration
FTND: Fagerström Test for Nicotine Dependence; FTND is a six item standard instrument measuring frequency and timing of smoking for assessing physical dependence to cigarettes. All items are summed with scores ranging from 0 to 10. FTND without cigarettes/day score ranges from 0 to 7. The higher the score, the greater the dependence on cigarettes.[5]
GERD: Gastroesophageal reflux disease
GI: Gastrointestinal
HMPMA/HBMA: 3-hydroxy-1-methylpropylmercapturic acid, biomarker for crotonaldehyde/methylvinyl ketone exposure
2-HPMA: 2-hydroxypropylmercapturic acid, biomarker for propylene oxide exposure
3-HPMA: 3-hydroxypropylmercapturic acid, biomarker for acrolein exposure
HR: Heart rate
IVR: Interactive Voice Response
MNWS: Minnesota Nicotine Withdrawal Scale; MNWS is an 8 item questionnaire assessing intensity of nicotine withdrawal with a 5 point scale ranging from None, Slight, Mild, Moderate, Severe scored as 0 to 4 with scores ranging from 0 to 32 with higher scores indicating more intense withdrawal symptoms.[6]
NIDA: National Institute for Drug Abuse
NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-specific nitrosamine
NMR: Nicotine metabolite ratio (3'-hydroxycotinine:cotinine)
NOS: Not otherwise specified
Total NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides, biomarker for NNK exposure
PAH: Polycyclic aromatic hydrocarbons
PheT: Phenanthrene tetraol, indicator of exposure to polycyclic aromatic hydrocarbons
QSU: Questionnaire of Smoking Urges-Brief*:* QSU-Brief is a 10 item scale measuring urge to smoke using a Likert type scale of 1=strongly disagree to 7= strongly agree. The scale is scored on with two factors: Factor 1 items reflect a strong desire and intention to smoke, with smoking perceived as rewarding for active smokers (scores range from 5 to 35). Factor 2 items represent an anticipation of relief from negative affect with an urgent desire to smoke (scores range from 5 to 35).[7,8]
SAE: Serious adverse event
SPMA: S-phenylmercapturic acid, biomarkers for benzene exposure
TNE: Total nicotine equivalents
VOC: Volatile organic compounds
WISDM: Brief Wisconsin Inventory of Smoking Dependence Motives: The Brief WISDM consists of 37 items using a Likert scale ranging from 1=Not true of me at all to 7=Extremely true of me. It includes 11 domains of smoking motivation with a two factor higher order primary and secondary dependence motives. The Primary Dependence Motives (PDM) includes four subscales: Automaticity, Loss of Control, Craving, and Tolerance. The Secondary Dependence Motives (SDM) includes seven scales: Affiliative Attachment, Cognitive Enhancement, Cue Exposure/Associative Processes, Social/Environmental Goads, Taste, Weight Control, and Affective Enhancement.[9,10] Total score ranges from 11 to 77; Primary Dependence Motives score ranges from 1 to 7; Secondary Dependence Motives score ranges from 1 to 7; higher scores signify greater dependence motives.

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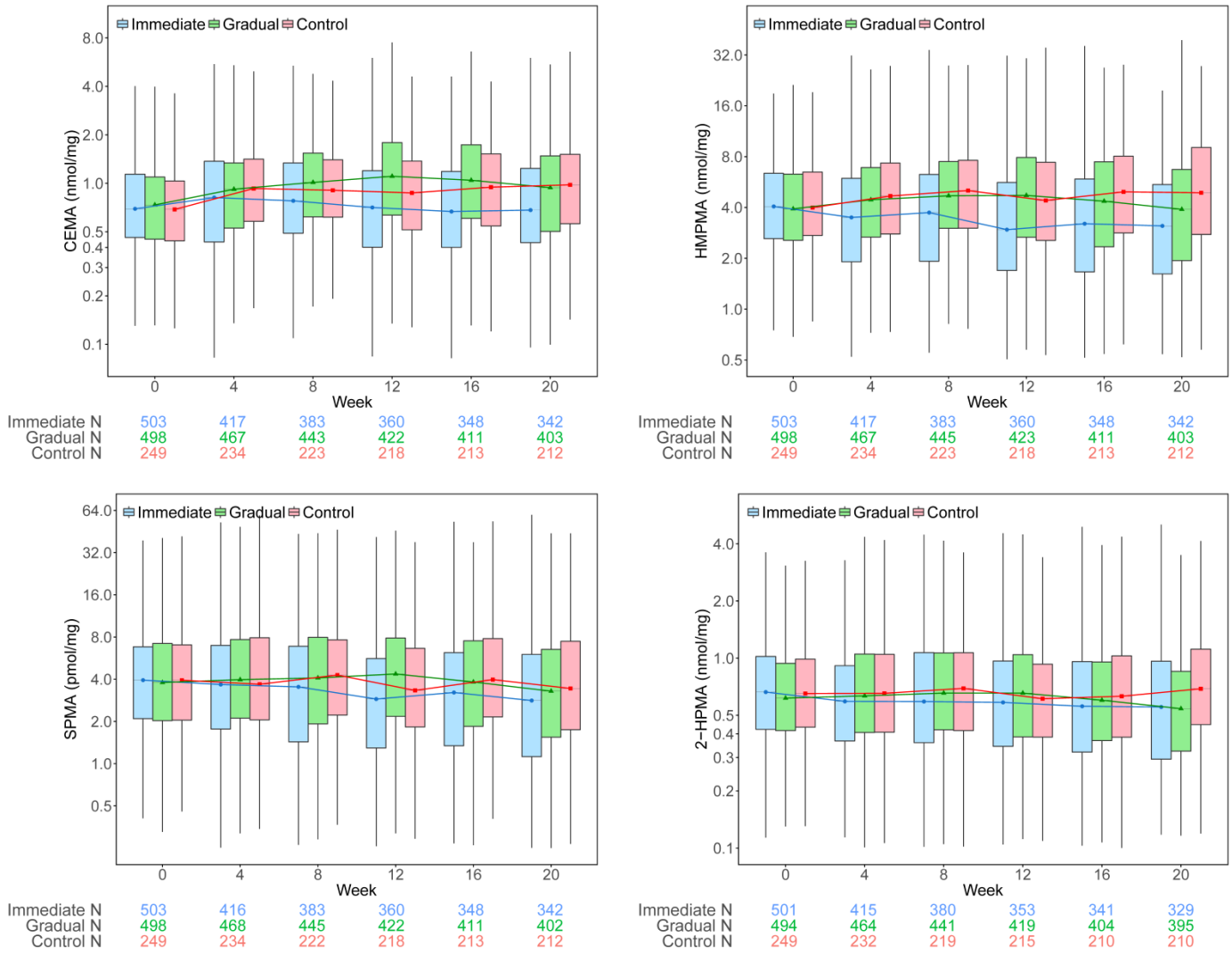
eFigure 1. Biomarkers of Exposure: Mercapturic Acids (Secondary Endpoints)[a,b]



[a]CEMA: 2-cyanoethylmercapturic acid, biomarker for acrylonitrile
HMPMA: 3-hydroxy-1-methylpropylmercapturic acid, biomarker for crotonaldehyde/methylvinyl ketone
SPMA: S-phenylmercapturic acid, biomarker for benzene
2-HPMA: 2-hydroxypropylmercapturic acid, biomarker for propylene oxide
Biomarkers are expressed per mg creatinine.
[b]The boxplot of the observed data (i.e., no imputation): the box shows the interquartile range (IQR) with the bottom and top indicating the 25th and 75th percentiles; the line inside the box indicating the median; the upper whisker extends from the top of the box to the largest value no further than 1.5 times IQR and the bottom whisker extends from the bottom of the box to the smallest value no further than 1.5 times IQR; the trajectory line connects the medians at each visit; boxplots at each visit are staggered to avoid superimposition. Number of participants may differ from the consort diagram due to inclusion of partial data collected from the participant within a dosing period prior to drop-out or missing values.

AUC analyses and interpretation are provided in eTable 1.

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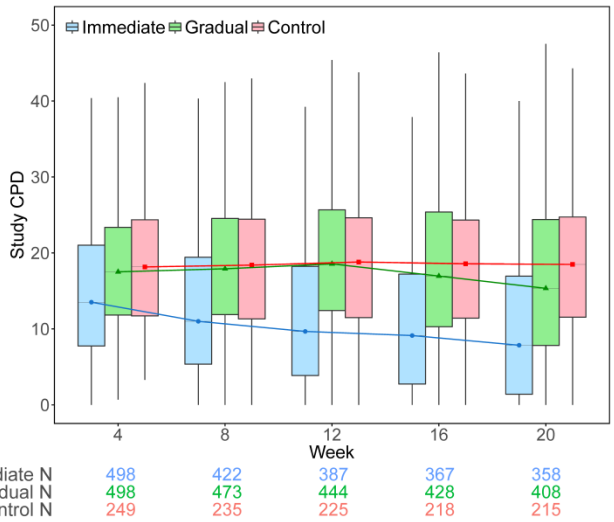
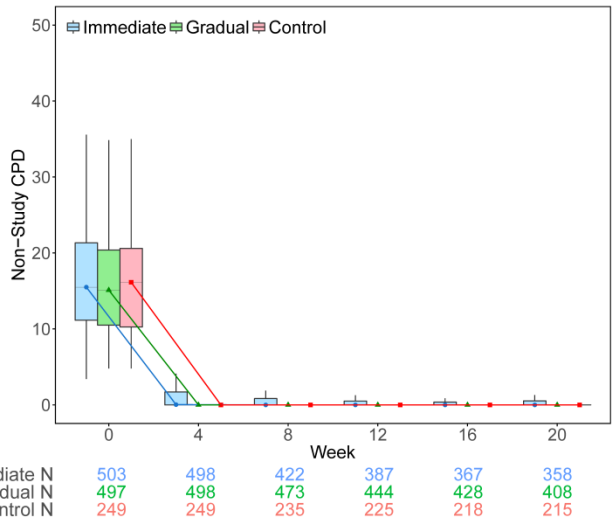
eFigure 2. Study and Non-Study Cigarettes Smoked per Day (CPD; Secondary Endpoints)[a]



Immediate N	498	422	387	367	358	
Gradual N	498	473	444	428	408	
Control N	249	235	225	218	215	



Immediate N	503	498	422	387	367	358
Gradual N	497	498	473	444	428	408
Control N	249	249	235	225	218	215

[a]The boxplot of the observed data (i.e., no imputation): the box shows the interquartile range (IQR) with the bottom and top indicating the 25th and 75th percentiles; the line inside the box indicating the median; the upper whisker extends from the top of the box to the largest value no further than 1.5 times IQR and the bottom whisker extends from the bottom of the box to the smallest value no further than 1.5 times IQR; the trajectory line connects the medians at each visit; boxplots at each visit are staggered to avoid superimposition.

AUC analyses and interpretation are provided in eTable1. Some of the sample sizes are larger than depicted in the Consort Diagram because partial Interactive Voice Response data prior to subject drop-out were included.

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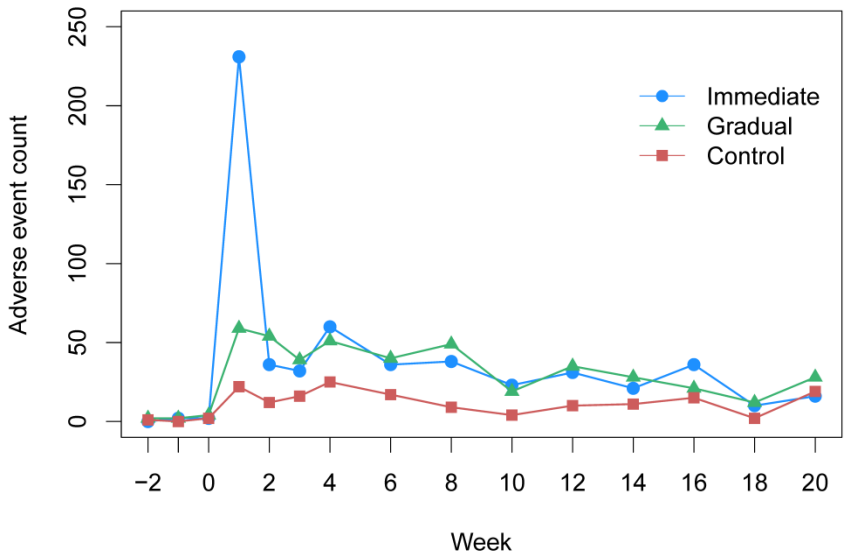
eFigure 3. Count of Related Adverse Events Reported by Week (Safety Endpoint) [a,b]



[a]Events that were Definitely Related, Probably Related or Relationship Unknown were counted on a per symptom basis. Related events in the same participants would be counted as multiple events. Baseline (-2, 0) includes only events in participants that went on to be randomized.
[b]Adverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

Summary: Significantly greater number of AEs was observed in the immediate versus gradual and control groups, particularly at Week 1. See eTable 4.

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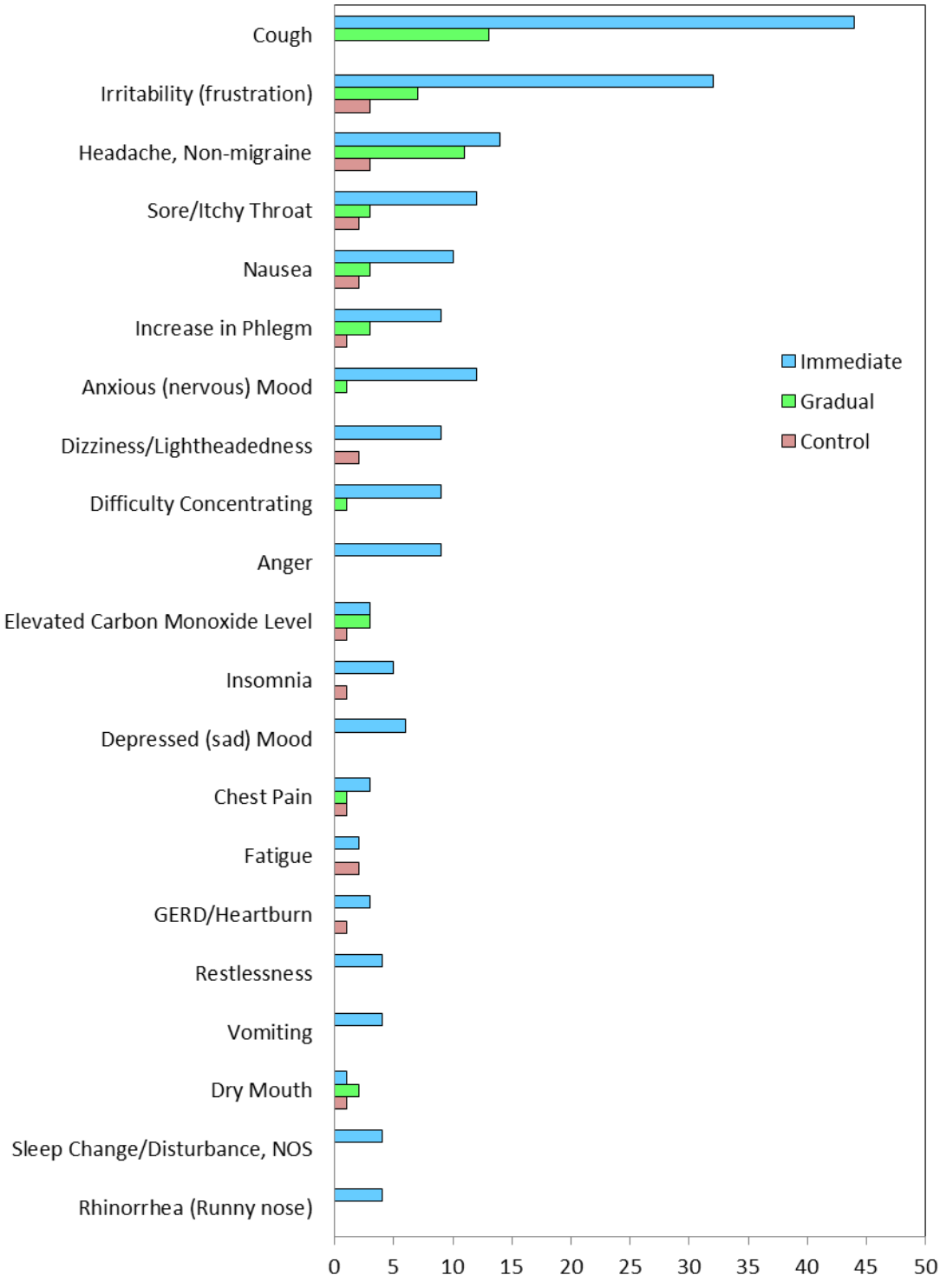
eFigure 4. Top 20 Adverse Events Reported at Week 1 (Safety Endpoint) [a,b]



[a]Events that were Definitely Related, Probably Related or Relationship Unknown were counted on a per symptom basis. Concurrent adverse events (e.g., cold symptoms) in the same participant would be counted as multiple events.
[b]Adverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

Summary: The greater rate of adverse symptoms in the immediate reduction group appears to be primarily related to symptoms of withdrawal from nicotine (e.g., mood and cough).

eTable 1. Biomarkers and Cigarettes per Day, Analysis of Area Under the Curve, by Different Missing Data Imputation Methods (Primary and Secondary Endpoints, Primary and Sensitivity Analyses)[a,b]

Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value
Primary Analysis Method: Multiple Imputation[d], Unadjusted[e]						
CO (ppm)	-4.06 (-4.89, -3.23)	<.0055	-3.38 (-4.40, -2.36)	<.0055	0.68 (-0.31, 1.67)	.18
3-HPMA (nmol/mg)	0.83 (0.77, 0.88)	<.0055	0.81 (0.75, 0.88)	<.0055	0.98 (0.91, 1.06)	.64
PheT (pmol/mg)	0.88 (0.83, 0.93)	<.0055	0.86 (0.81, 0.92)	<.0055	0.98 (0.92, 1.04)	.52
TNE (nmol/mg)	0.61 (0.55, 0.68)	<.00057	0.42 (0.37, 0.48)	<.00057	0.69 (0.61, 0.78)	<.00057
Total NNAL (pmol/mg)	0.77 (0.71, 0.84)	<.00057	0.68 (0.62, 0.76)	<.00057	0.88 (0.80, 0.98)	.014
CEMA (nmol/mg)	0.66 (0.61, 0.72)	<.00057	0.71 (0.64, 0.78)	<.00057	1.07 (0.97, 1.18)	.20
HMPMA (nmol/mg)	0.79 (0.74, 0.85)	<.00057	0.77 (0.71, 0.84)	<.00057	0.98 (0.90, 1.06)	.58
SPMA (pmol/mg)	0.75 (0.69, 0.82)	<.00057	0.78 (0.71, 0.87)	<.00057	1.04 (0.94, 1.15)	.43
2-HPMA (nmol/mg)	0.92 (0.86, 1.00)	.042	0.84 (0.77, 0.92)	<.00057	0.91 (0.83, 0.99)	.032
Cigarettes/day total	-5.18 (-5.97, -4.39)	<.00057	-5.47 (-6.44, -4.50)	<.00057	-0.29 (-1.26, 0.68)	.55
Cigarettes/day study	-6.70 (-7.54, -5.86)	<.00057	-6.82 (-7.84, -5.80)	<.00057	-0.12 (-1.14, 0.89)	.81
Cigarettes/day non-study	1.58 (1.12, 2.04)	<.00057	1.46 (0.87, 2.05)	<.00057	-0.12 (-0.72, 0.48)	.69
Last Observation Carried Forward Imputation[f], Unadjusted[e]						
CO (ppm)	-3.20 (-4.06, -2.35)	<.001	-2.74 (-3.79, -1.69)	<.001	0.46 (-0.59, 1.51)	.39
3-HPMA (nmol/mg)	0.84 (0.79, 0.89)	<.001	0.81 (0.76, 0.87)	<.001	0.96 (0.90, 1.04)	.32
PheT (pmol/mg)	0.90 (0.86, 0.95)	<.001	0.89 (0.84, 0.95)	<.001	0.98 (0.93, 1.05)	.62
TNE (nmol/mg)	0.64 (0.58, 0.70)	<.001	0.46 (0.41, 0.52)	<.001	0.72 (0.65, 0.81)	<.001
Total NNAL (pmol/mg)	0.79 (0.74, 0.85)	<.001	0.71 (0.65, 0.78)	<.001	0.90 (0.82, 0.99)	.023
CEMA (nmol/mg)	0.69 (0.65, 0.74)	<.001	0.73 (0.67, 0.79)	<.001	1.05 (0.96, 1.14)	.29
HMPMA (nmol/mg)	0.80 (0.75, 0.85)	<.001	0.77 (0.71, 0.83)	<.001	0.96 (0.89, 1.03)	.28
SPMA (pmol/mg)	0.79 (0.73, 0.85)	<.001	0.80 (0.73, 0.88)	<.001	1.02 (0.93, 1.11)	.74
2-HPMA (nmol/mg)	0.92 (0.86, 0.99)	.030	0.81 (0.75, 0.89)	<.001	0.88 (0.81, 0.96)	.004
Cigarettes/day total	-5.22 (-6.10, -4.35)	<.001	-5.82 (-6.89, -4.75)	<.001	-0.60 (-1.67, 0.47)	.27
Cigarettes/day study	-7.12 (-8.08, -6.17)	<.001	-7.61 (-8.78, -6.45)	<.001	-0.49 (-1.66, 0.68)	.41
Cigarettes/day non-study	1.98 (1.47, 2.50)	<.001	1.87 (1.24, 2.50)	<.001	-0.11 (-0.74, 0.52)	.73
Baseline Imputation[g], Unadjusted[e]						
CO (ppm)	-3.48 (-4.19, -2.77)	<.001	-2.67 (-3.57, -1.82)	<.001	0.79 (-0.08, 1.66)	.077
3-HPMA (nmol/mg)	0.85 (0.81, 0.90)	<.001	0.83 (0.78, 0.89)	<.001	0.98 (0.92, 1.05)	.61
PheT (pmol/mg)	0.91 (0.87, 0.95)	<.001	0.89 (0.84, 0.94)	<.001	0.98 (0.93, 1.04)	.54
TNE (nmol/mg)	0.66 (0.61, 0.73)	<.001	0.49 (0.44, 0.54)	<.001	0.73 (0.66, 0.82)	<.001
Total NNAL (pmol/mg)	0.80 (0.75, 0.86)	<.001	0.73 (0.67, 0.80)	<.001	0.91 (0.84, 0.99)	.034
CEMA (nmol/mg)	0.70 (0.66, 0.75)	<.001	0.74 (0.68, 0.81)	<.001	1.06 (0.97, 1.15)	.19
HMPMA (nmol/mg)	0.80 (0.76, 0.85)	<.001	0.79 (0.73, 0.84)	<.001	0.98 (0.92, 1.05)	.62
SPMA (pmol/mg)	0.79 (0.74, 0.85)	<.001	0.82 (0.75, 0.90)	<.001	1.04 (0.96, 1.14)	.35

Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value
2-HPMA (nmol/mg)	0.92 (0.86, 0.99)	.018	0.84 (0.78, 0.91)	<.001	0.91 (0.84, 0.99)	.026
Cigarettes/day total	-4.52 (-5.22, -3.81)	<.001	-4.53 (-5.4, -3.67)	<.001	-0.02 (-0.88, 0.85)	.97
Multiple Imputation[d], Adjusted[h]						
CO (ppm)	-4.22 (-5.04, -3.41)	<.001	-3.59 (-4.59, -2.60)	<.001	0.63 (-0.34, 1.60)	.20
3-HPMA (nmol/mg)	0.81 (0.76, 0.87)	<.001	0.80 (0.74, 0.86)	<.001	0.98 (0.91, 1.05)	.60
PheT (pmol/mg)	0.88 (0.83, 0.93)	<.001	0.86 (0.81, 0.92)	<.001	0.98 (0.92, 1.05)	.56
TNE (nmol/mg)	0.60 (0.54, 0.67)	<.001	0.42 (0.37, 0.47)	<.001	0.69 (0.62, 0.78)	<.001
Total NNAL (pmol/mg)	0.75 (0.69, 0.82)	<.001	0.67 (0.60, 0.74)	<.001	0.89 (0.81, 0.98)	.013
CEMA (nmol/mg)	0.65 (0.60, 0.71)	<.001	0.70 (0.63, 0.77)	<.001	1.07 (0.97, 1.18)	.15
HMPMA (nmol/mg)	0.78 (0.73, 0.83)	<.001	0.76 (0.70, 0.82)	<.001	0.97 (0.90, 1.05)	.51
SPMA (pmol/mg)	0.74 (0.68, 0.81)	<.001	0.77 (0.70, 0.85)	<.001	1.05 (0.95, 1.15)	.39
2-HPMA (nmol/mg)	0.92 (0.85, 0.99)	.023	0.84 (0.77, 0.91)	<.001	0.91 (0.84, 0.99)	.038
Cigarettes/day total	-5.28 (-6.06, -4.50)	<.001	-5.48 (-6.44, -4.51)	<.001	-0.20 (-1.15, 0.76)	.68
Cigarettes/day study	-6.79 (-7.62, -5.96)	<.001	-6.83 (-7.84, -5.82)	<.001	-0.04 (-1.04, 0.96)	.93
Cigarettes/day non-study	1.56 (1.10, 2.03)	<.001	1.46 (0.87, 2.06)	<.001	-0.10 (-0.70, 0.49)	.74
Last Observation Carried Forward Imputation[f], Adjusted[h]						
CO (ppm)	-3.46 (-4.32, -2.60)	<.001	-2.95 (-4.00, -1.90)	<.001	0.51 (-0.55, 1.56)	.35
3-HPMA (nmol/mg)	0.83 (0.78, 0.87)	<.001	0.80 (0.75, 0.86)	<.001	0.97 (0.90, 1.04)	.39
PheT (pmol/mg)	0.90 (0.86, 0.95)	<.001	0.89 (0.84, 0.95)	<.001	0.99 (0.93, 1.05)	.70
TNE (nmol/mg)	0.64 (0.58, 0.70)	<.001	0.46 (0.41, 0.51)	<.001	0.72 (0.65, 0.81)	<.001
Total NNAL (pmol/mg)	0.78 (0.73, 0.84)	<.001	0.71 (0.65, 0.77)	<.001	0.90 (0.83, 0.99)	.026
CEMA (nmol/mg)	0.67 (0.63, 0.72)	<.001	0.71 (0.65, 0.78)	<.001	1.06 (0.97, 1.15)	.22
HMPMA (nmol/mg)	0.78 (0.74, 0.83)	<.001	0.75 (0.70, 0.81)	<.001	0.96 (0.90, 1.04)	.32
SPMA (pmol/mg)	0.78 (0.72, 0.84)	<.001	0.79 (0.72, 0.87)	<.001	1.01 (0.92, 1.11)	.84
2-HPMA (nmol/mg)	0.92 (0.86, 0.99)	.020	0.80 (0.74, 0.88)	<.001	0.88 (0.80, 0.96)	.003
Cigarettes/day total	-5.37 (-6.26, -4.48)	<.001	-5.82 (-6.90, -4.74)	<.001	-0.45 (-1.54, 0.63)	.41
Cigarettes/day study	-7.31 (-8.27, -6.34)	<.001	-7.65 (-8.82, -6.47)	<.001	-0.34 (-1.52, 0.84)	.57
Cigarettes/day non-study	2.03 (1.50, 2.56)	<.001	1.91 (1.27, 2.56)	<.001	-0.12 (-0.76, 0.53)	.72
Baseline Imputation[g], Adjusted[h]						
CO (ppm)	-3.73 (-4.44, -3.02)	<.001	-2.95 (-3.81, -2.08)	<.001	0.78 (-0.09, 1.65)	.077
3-HPMA (nmol/mg)	0.84 (0.80, 0.88)	<.001	0.82 (0.77, 0.88)	<.001	0.98 (0.92, 1.05)	.62
PheT (pmol/mg)	0.90 (0.86, 0.95)	<.001	0.89 (0.84, 0.94)	<.001	0.98 (0.93, 1.04)	.56
TNE (nmol/mg)	0.66 (0.61, 0.72)	<.001	0.49 (0.44, 0.54)	<.001	0.73 (0.66, 0.82)	<.001
Total NNAL (pmol/mg)	0.79 (0.74, 0.85)	<.001	0.73 (0.67, 0.79)	<.001	0.91 (0.84, 0.99)	.035
CEMA (nmol/mg)	0.69 (0.64, 0.73)	<.001	0.73 (0.67, 0.79)	<.001	1.06 (0.98, 1.15)	.15
HMPMA (nmol/mg)	0.79 (0.74, 0.83)	<.001	0.77 (0.72, 0.83)	<.001	0.98 (0.92, 1.05)	.63
SPMA (pmol/mg)	0.78 (0.73, 0.84)	<.001	0.81 (0.74, 0.88)	<.001	1.04 (0.95, 1.13)	.38
2-HPMA (nmol/mg)	0.92 (0.86, 0.98)	.011	0.83 (0.77, 0.90)	<.001	0.91 (0.84, 0.99)	.022
Cigarettes/day total	-4.64 (-5.35, -3.93)	<.001	-4.51 (-5.38, -3.64)	<.001	0.13 (-0.74, 1.00)	.77

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[a] *P*s<.0055 were considered significant for primary (CO, 3-HPMA, PheT) and <.00057 for secondary (TNE, total NNAL, CEMA, HMPMA, SPMA, 2-HPMA, and CPDs) endpoints for the primary analysis method (multiple imputation, unadjusted). See abbreviation glossary for name of acronyms.
Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249); see Figure 2, eFigures 1 and 2 for the sample size at each visit.
[b]Area under the curve (AUC) scaled by time (i.e., time-scaled AUC); the unit is the same as its original variable; biomarkers are expressed as per mg creatinine.
[c]Mean difference in original scale for carbon monoxide (CO) and cigarettes/day and ratio of geometric means for the other outcomes
[d]Missing values imputed with multiple imputation using the Markov Chain Monte Carlo (MCMC) method.
[e]Unadjusted: Linear regression unadjusted for any covariates except for the corresponding baseline measure; log-transformation was used for all the outcome variables and the corresponding baseline measures except for CO and cigarettes/day variables.
[f]Missing values imputed with the last observation carried forward (LOCF) method for dropouts and with trapezoidal rule for intermittent missing.
[g]Missing values imputed with baseline value for dropouts and with trapezoidal rule for intermittent missing; this imputation method was not applicable to cigarettes/day study or cigarettes/day non-study because there were no corresponding measurements at baseline.
[h]Adjusted: Linear regression adjusted for the corresponding baseline level of the outcome variable, study site, together with any baseline variables which were different between treatment arms at p<0.20 (employment, Fagerstrom Test for Nicotine Dependence, and serum nicotine metabolic ratio); log-transformation was used for the outcome variables and the corresponding baseline measures except for CO and cigarettes/day variables.

Summary: For primary (CO, 3HPMA, PheT) and all other secondary endpoints, significant differences were observed between immediate versus gradual nicotine reduction and versus control groups, with lower overall exposures in the immediate reduction group, with the exception of 2-HPMA which showed no significant differences between immediate versus gradual group. However, significantly higher mean numbers of non-study cigarettes were smoked in the immediate versus gradual and control groups. Very few differences were observed between gradual versus control group, with the exception of TNE which showed lower overall exposure in the gradual reduction group. These patterns of results were generally observed regardless of the method of imputation or whether the analyses were adjusted or unadjusted. These results indicate lower overall toxicant exposures in the immediate versus gradual nicotine reduction group (ranging from 12% to 34%) and lower overall nicotine exposure (about 40%).

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eTable 2. Cigarette-Free Days (Secondary and Exploratory Endpoints, Primary Analysis)[a]

Measures	Immediate	Gradual	Control	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	No. (%) or Mean (SD)	No. (%) or Mean (SD)	No. (%) or Mean (SD)	Estimated OR/IRR (95% CI)	*P* Value	Estimated OR/IRR (95% CI)	*P* Value	Estimated OR/IRR (95% CI)	*P* Value
Any one cigarette-free day during weeks 0-20, No. (%)[b]	182 (36%)	138 (28%)	59 (24%)	1.48 (1.13, 1.93)	.004	1.83 (1.29, 2.58)	.006	1.23 (0.87, 1.76)	.24
Count of cigarette-free days during weeks 0-20, mean (SD)[c]	10.9 (27.0)	3.1 (10.4)	3.1 (13.5)	3.57 (2.34, 5.43)	<.00057	3.48 (2.08, 5.84)	<.00057	0.98 (0.58, 1.64)	.93
CO-verified (<6 ppm) 7 cigarette free days at 20 weeks, No. (%)[b]	37 (7%)	15 (3%)	6 (2%)	2.56 (1.38, 4.72)	<.0167	3.22 (1.34, 7.73)	<.0167	1.26 (0.48, 3.28)	.64

[a]Any cigarette-free day and count of cigarette-free days during weeks 0-20 are secondary endpoints; CO-verified 7 cigarette free days at week 20 (yes/no) is an exploratory endpoint; *P*s<.00057 were considered significant for secondary and <.0167 for exploratory endpoints; Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249). See abbreviation glossary for name of acronyms.
[b]Odds ratio (OR) was estimated based on unadjusted analysis; no abstinence being assumed for days with missing Interactive Voice Response (IVR) data.
[c]Incidence rate ratio (IRR) was estimated based on unadjusted negative binomial regression; no abstinence being assumed for days with missing IVR data.

Summary: Significantly greater number of cigarette-free days but not proportion of any one cigarette-free day was observed for immediate versus gradual nicotine reduction and control groups. Exploratory analyses showed significantly higher rate of CO-verified 7 cigarette free days at Week 20 for immediate versus gradual and control groups. No significant differences were observed for the gradual versus control group.

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eTable 3. Minnesota Nicotine Withdrawal Scale (MNWS) Scores, Questionnaire on Smoking Urges-Brief (QSU) Factor 1 and 2, and Center for Epidemiologic Studies Depression Scale (CESD) by Weeks (Secondary and Safety Endpoints, Primary and Secondary Analyses)[a]

Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Primary Analysis Method: Linear Mixed Effects Model 1[b]							
MNWS total score	1	2.21 (1.62, 2.79)	<.00057*	2.39 (1.68, 3.10)	<.00057*	0.18 (-0.53, 0.89)	.61
	2	0.69 (0.10, 1.29)	.022	1.18 (0.45, 1.90)	.001	0.49 (-0.23, 1.20)	.18
	3	0.82 (0.22, 1.42)	.008	1.14 (0.40, 1.87)	.002	0.32 (-0.40, 1.04)	.39
	4	0.71 (0.12, 1.31)	.019	0.27 (-0.45, 1.00)	.46	-0.44 (-1.16, 0.28)	.23
	6	0.15 (-0.46, 0.76)	.63	0.22 (-0.52, 0.95)	.57	0.07 (-0.66, 0.79)	.86
	8	0.06 (-0.55, 0.67)	.85	0.08 (-0.66, 0.83)	.82	0.02 (-0.70, 0.75)	.95
	10	-0.06 (-0.69, 0.56)	.84	0.57 (-0.18, 1.32)	.14	0.64 (-0.10, 1.37)	.091
	12	-0.10 (-0.73, 0.52)	.74	0.54 (-0.21, 1.29)	.16	0.64 (-0.09, 1.38)	.086
	14	-0.34 (-0.96, 0.29)	.30	0.02 (-0.73, 0.78)	.95	0.36 (-0.38, 1.10)	.34
	16	-0.33 (-0.96, 0.30)	.30	0.12 (-0.63, 0.88)	.75	0.46 (-0.28, 1.19)	.23
	18	-0.05 (-0.68, 0.58)	.87	0.04 (-0.72, 0.80)	.91	0.09 (-0.65, 0.84)	.80
	20	-0.19 (-0.82, 0.44)	.56	-0.43 (-1.19, 0.32)	.26	-0.25 (-0.99, 0.49)	.51
Study cigarette QSU Factor 1[c]	1	-1.43 (-2.36, -0.49)	.003	-1.04 (-2.18, 0.10)	.074	0.39 (-0.75, 1.52)	.50
	2	-2.71 (-3.65, -1.76)	<.00057*	-2.69 (-3.84, -1.54)	<.00057*	0.02 (-1.12, 1.16)	.97
	3	-2.37 (-3.33, -1.42)	<.00057*	-2.30 (-3.47, -1.14)	<.001	0.07 (-1.07, 1.22)	.90
	4	-2.43 (-3.38, -1.48)	<.00057*	-3.11 (-4.26, -1.95)	<.00057*	-0.67 (-1.81, 0.47)	.25
	6	-3.50 (-4.46, -2.54)	<.00057*	-3.70 (-4.87, -2.53)	<.00057*	-0.20 (-1.36, 0.95)	.73
	8	-3.55 (-4.51, -2.58)	<.00057*	-3.78 (-4.96, -2.61)	<.00057*	-0.23 (-1.39, 0.92)	.69
	10	-3.97 (-4.95, -2.99)	<.00057*	-4.01 (-5.19, -2.82)	<.00057*	-0.04 (-1.21, 1.13)	.95
	12	-4.10 (-5.08, -3.12)	<.00057*	-3.93 (-5.11, -2.75)	<.00057*	0.17 (-0.99, 1.33)	.78
	14	-3.77 (-4.76, -2.78)	<.00057*	-4.20 (-5.40, -3.01)	<.00057*	-0.43 (-1.60, 0.74)	.47
	16	-4.27 (-5.25, -3.28)	<.00057*	-4.88 (-6.07, -3.69)	<.00057*	-0.61 (-1.78, 0.55)	.30
	18	-3.68 (-4.67, -2.69)	<.00057*	-4.74 (-5.93, -3.54)	<.00057*	-1.06 (-2.23, 0.12)	.077
	20	-2.57 (-3.56, -1.58)	<.00057*	-4.62 (-5.81, -3.43)	<.00057*	-2.05 (-3.22, -0.88)	<.001
Study cigarette QSU Factor 2[c]	1	0.07 (-0.53, 0.68)	.81	0.03 (-0.71, 0.78)	.93	-0.04 (-0.78, 0.70)	.91
	2	-0.82 (-1.44, -0.20)	.009	-0.75 (-1.51, 0.00)	.049	0.06 (-0.68, 0.81)	.86
	3	-0.75 (-1.38, -0.13)	.018	-0.57 (-1.33, 0.19)	.14	0.18 (-0.56, 0.93)	.63
	4	-0.97 (-1.59, -0.35)	.002	-1.30 (-2.05, -0.54)	<.001	-0.33 (-1.07, 0.42)	.39
	6	-1.24 (-1.86, -0.61)	<.001	-1.18 (-1.95, -0.42)	.002	0.05 (-0.70, 0.81)	.89
	8	-1.15 (-1.78, -0.52)	<.001	-0.97 (-1.74, -0.21)	.013	0.17 (-0.58, 0.93)	.65
	10	-1.55 (-2.19, -0.91)	<.00057*	-1.15 (-1.92, -0.37)	.004	0.40 (-0.36, 1.16)	.30
	12	-1.55 (-2.19, -0.91)	<.00057*	-1.22 (-1.99, -0.45)	.002	0.33 (-0.43, 1.09)	.39
	14	-1.48 (-2.13, -0.84)	<.00057*	-1.50 (-2.27, -0.72)	<.001	-0.01 (-0.78, 0.75)	.97

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Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
	16	-1.91 (-2.55, -1.26)	<.00057*	-2.10 (-2.88, -1.32)	<.00057	-0.20 (-0.96, 0.57)	.61
	18	-1.71 (-2.35, -1.06)	<.001	-1.60 (-2.38, -0.82)	<.001	0.11 (-0.66, 0.87)	.78
	20	-1.22 (-1.86, -0.57)	<.001	-1.68 (-2.45, -0.90)	<.001	-0.46 (-1.22, 0.30)	.24
CESD	4	1.45 (0.46, 2.45)	.004	0.39 (-0.82, 1.60)	.52	-1.06 (-2.24, 0.13)	.080
	8	1.22 (0.20, 2.25)	.019	0.32 (-0.92, 1.56)	.62	-0.91 (-2.11, 0.30)	.14
	12	1.14 (0.10, 2.18)	.032	1.14 (-0.11, 2.40)	.073	0.00 (-1.22, 1.22)	>.99
	16	0.83 (-0.22, 1.89)	.12	0.16 (-1.10, 1.43)	.80	-0.67 (-1.90, 0.56)	.28
	20	1.20 (0.14, 2.26)	.026	0.58 (-0.68, 1.85)	.37	-0.61 (-1.85, 0.62)	.33
Linear Mixed Effects Model 2[d]							
MNWS total score	1	2.24 (1.64, 2.84)	<.001	2.34 (1.61, 3.06)	<.001	0.10 (-0.63, 0.82)	.80
	2	0.72 (0.12, 1.33)	.019	1.16 (0.42, 1.89)	.002	0.44 (-0.29, 1.16)	.24
	3	0.83 (0.22, 1.45)	.008	1.06 (0.31, 1.80)	.005	0.22 (-0.51, 0.95)	.55
	4	0.73 (0.13, 1.34)	.018	0.21 (-0.53, 0.95)	.58	-0.53 (-1.26, 0.20)	.16
	6	0.21 (-0.41, 0.82)	.51	0.15 (-0.60, 0.90)	.69	-0.05 (-0.79, 0.69)	.89
	8	0.06 (-0.56, 0.68)	.85	-0.02 (-0.77, 0.73)	.96	-0.08 (-0.82, 0.66)	.83
	10	-0.13 (-0.76, 0.50)	.69	0.45 (-0.31, 1.21)	.25	0.58 (-0.17, 1.33)	.13
	12	-0.13 (-0.76, 0.50)	.69	0.43 (-0.33, 1.18)	.27	0.55 (-0.19, 1.30)	.15
	14	-0.33 (-0.97, 0.31)	.31	-0.12 (-0.88, 0.65)	.77	0.22 (-0.53, 0.97)	.57
	16	-0.30 (-0.94, 0.33)	.35	0.04 (-0.72, 0.81)	.92	0.34 (-0.41, 1.09)	.37
	18	-0.02 (-0.66, 0.62)	.96	-0.03 (-0.80, 0.74)	.93	-0.01 (-0.77, 0.74)	.97
	20	-0.18 (-0.82, 0.46)	.58	-0.46 (-1.23, 0.31)	.24	-0.28 (-1.03, 0.47)	.47
Study cigarette QSU Factor 1[c]	1	-1.54 (-2.46, -0.61)	.001	-1.23 (-2.36, -0.11)	.032	0.30 (-0.81, 1.42)	.59
	2	-2.87 (-3.81, -1.94)	<.001	-2.93 (-4.07, -1.79)	<.001	-0.06 (-1.19, 1.07)	.92
	3	-2.39 (-3.33, -1.44)	<.001	-2.50 (-3.64, -1.35)	<.001	-0.11 (-1.24, 1.03)	.85
	4	-2.53 (-3.47, -1.58)	<.001	-3.23 (-4.37, -2.09)	<.001	-0.71 (-1.83, 0.42)	.22
	6	-3.52 (-4.47, -2.56)	<.001	-3.92 (-5.08, -2.77)	<.001	-0.41 (-1.55, 0.73)	.48
	8	-3.60 (-4.56, -2.64)	<.001	-3.99 (-5.15, -2.83)	<.001	-0.39 (-1.53, 0.75)	.50
	10	-4.08 (-5.06, -3.11)	<.001	-4.23 (-5.41, -3.06)	<.001	-0.15 (-1.30, 1.00)	.80
	12	-4.26 (-5.24, -3.29)	<.001	-4.16 (-5.33, -2.99)	<.001	0.11 (-1.04, 1.25)	.86
	14	-3.96 (-4.94, -2.98)	<.001	-4.51 (-5.69, -3.33)	<.001	-0.55 (-1.71, 0.61)	.35
	16	-4.46 (-5.44, -3.49)	<.001	-5.11 (-6.28, -3.93)	<.001	-0.64 (-1.80, 0.51)	.27
	18	-3.90 (-4.88, -2.91)	<.001	-5.01 (-6.19, -3.83)	<.001	-1.11 (-2.27, 0.05)	.060
	20	-2.84 (-3.82, -1.86)	<.001	-4.92 (-6.10, -3.74)	<.001	-2.07 (-3.23, -0.92)	<.001
Study cigarette QSU Factor 2[c]	1	0.11 (-0.49, 0.72)	.72	0.04 (-0.70 0.77)	.92	-0.07 (-0.81, 0.66)	.84
	2	-0.81 (-1.43, -0.20)	.009	-0.77 (-1.52, -0.03)	.041	0.04 (-0.70, 0.78)	.92
	3	-0.69 (-1.31, -0.07)	.029	-0.54 (-1.29, 0.22)	.16	0.15 (-0.59, 0.89)	.68
	4	-0.92 (-1.53, -0.30)	.003	-1.30 (-2.04, -0.55)	<.001	-0.38 (-1.12, 0.36)	.31
	6	-1.14 (-1.77, -0.52)	<.001	-1.21 (-1.97, -0.45)	.002	-0.07 (-0.81, 0.68)	.86

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Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
	8	-1.02 (-1.65, -0.40)	.001	-1.01 (-1.77, -0.25)	.009	0.02 (-0.73, 0.76)	.97
	10	-1.52 (-2.15, -0.88)	<.001	-1.20 (-1.96, -0.43)	.002	0.32 (-0.43, 1.08)	.40
	12	-1.52 (-2.15, -0.89)	<.001	-1.23 (-1.99, -0.46)	.002	0.29 (-0.46, 1.04)	.45
	14	-1.52 (-2.16, -0.88)	<.001	-1.60 (-2.37, -0.83)	<.001	-0.08 (-0.83, 0.68)	.84
	16	-1.87 (-2.51, -1.23)	<.001	-2.13 (-2.89, -1.36)	<.001	-0.26 (-1.01, 0.50)	.50
	18	-1.68 (-2.33, -1.04)	<.001	-1.69 (-2.46, -0.92)	<.001	-0.01 (-0.76, 0.75)	.99
	20	-1.23 (-1.87, -0.59)	<.001	-1.75 (-2.52, -0.98)	<.001	-0.51 (-1.27, 0.24)	.18
CESD	4	1.45 (0.44, 2.46)	.005	0.39 (-0.83, 1.62)	.53	-1.05 (-2.26, 0.15)	.086
	8	1.07 (0.03, 2.11)	.043	0.17 (-1.09, 1.42)	.79	-0.90 (-2.13, 0.32)	.15
	12	1.11 (0.06, 2.17)	.039	0.93 (-0.34, 2.20)	.15	-0.18 (-1.42, 1.05)	.77
	16	0.77 (-0.29, 1.84)	.16	-0.01 (-1.28, 1.27)	.99	-0.78 (-2.02, 0.46)	.22
	20	1.14 (0.07, 2.21)	.038	0.62 (-0.66, 1.90)	.34	-0.52 (-1.77, 0.73)	.41
Change from Baseline at Week 1 and 4, Causal Effect[e]							
MNWS total score	1	2.08 (1.21, 2.88)	.008	2.35 (1.37, 3.3)	.008	0.27 (-0.37, 0.92)	.40

[a]*P*s<.00057 were considered significant for secondary endpoints (MNWS, QSU Factors 1 and 2) and 0.0167 for safety endpoint (CESD); p-values shown in this table are raw p-values without adjustment; p-values remained significant after adjustment for multiple time points using the Hommel method are indicated with * for the primary analysis method (linear mixed model, unadjusted); Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249); see Figure 3 for the sample size at each visit for MNWS and QSU Factors 1 and 2 (Factors 1 and 2's sample sizes are the same); the sample size of CESD for Immediate, Gradual and Control at the Screening Visit: 503, 498, 249, Week 4: 416, 468, 234, Week 8: 381, 445, 222, Week 12: 360, 423, 218, Week 16: 347, 410, 214, Week 20: 342, 403, 213; see abbreviation glossary for range of scores.

[b]Linear mixed effects model 1: linear mixed model for repeated measures with fixed effects of treatment, week, and treatment-week interaction, adjusting for corresponding baseline values; no imputation.

[c]Factor 1: anticipation of pleasurable effects from smoking; Factor 2: anticipation of relief from negative affect and withdrawal symptoms.

[d]Linear mixed effects model 2: linear mixed model for repeated measures with fixed effects of treatment, week, and treatment-week interaction, adjusting for corresponding baseline values, study site, together with any baseline variables which were different between treatment arms at p<0.20 (employment, Fagerstrom Test for Nicotine Dependence, and serum nicotine metabolic ratio); no imputation.

[e]The impact of adherence to only using study cigarettes was estimated using the compliance unsure reweighted estimator (CURE).[11] The causal effect refers to the effect that would have been observed if all participants were compelled to adhere with the protocol and smoke only study cigarettes. This is in contrast to the effect that is observed if analysis is completed using only the adherent subjects (i.e. the per protocol effect). Participants that adhere to the protocol are likely different that non-adherent participants on a number of covariates and, as a result, different than the original study population. Therefore, the population of adherent participants must be re-weighted to reflect the covariate distribution of the entire study population, which results in an estimate of the treatment effect that would have been observed had all subjects been adherent. The methodology used in this manuscript (the CURE estimator) is an extension of the inverse probability of compliance weighted estimator to the case where our measure of compliance is continuous and potentially measured with error (i.e. a biomarker). Outcomes were evaluated as the absolute change or percent reduction from baseline. Adherence in the immediate and gradual reduction groups was identified using total nicotine equivalents ($\leq$ 6 nmol/ml) at week 20.[12] Adherence could not be confirmed for participants lacking week 20 visit data and, therefore, participants that did not have data at week 20 were not included in the analysis. Participants in the control group were treated as compliant regardless of non-study cigarette use because control cigarettes have similar nicotine content to commercial cigarettes. Baseline covariates associated with adherence at week 20 and outcome at week 20 were identified using the LASSO with the tuning parameter identified by cross-validation and the final analysis adjusted for baseline covariates that were associated with both the outcome and adherence or that were associated with only the outcome. Confidence intervals and p-values were calculated using the non-parametric bootstrap.

Summary: Significantly higher mean scores for MNWS were observed for the immediate versus gradual nicotine reduction and control group at Week 1. No significant difference in mean severity of withdrawal was observed between gradual versus control group. Generally, lower mean scores were observed for the immediate versus gradual and control groups on Factor 1 of the QSU (measure of anticipating pleasurable effects from smoking). For Factor 2 QSU (measure of anticipation of relief from negative affect and withdrawal symptoms), significant differences were not observed between immediate versus gradual reduction group until after several weeks; therefore 0.4 mg nicotine dose might initially provide similar anticipation of relief from withdrawal symptoms or negative affect as the gradual reduction group, but subsequently provides lower anticipation of relief. No significant differences in QSU scores were observed between gradual versus control group. Sensitivity analysis showed similar pattern of results. In general no differences were observed across the groups on CESD scores. Overall, these results would indicate that the immediate reduction group may be associated with some degree of discomfort and less pleasure from the assigned cigarettes. No safety concerns were related to depression scores.

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eTable 4. Adverse Events Counts, Out of Range Blood Pressure or Heart Rate, and Elevated Carbon Monoxide (Safety Endpoints)[a,b]

Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Estimated IRR/OR (95% CI)	*P* Value	Estimated IRR/OR (95% CI)	*P* Value	Estimated IRR/OR (95% CI)	*P* Value
Total AE count during the experimental period[c]	1-20	1.62 (1.29, 2.04)	<.0167	2.33 (1.74, 3.11)	<.0167	1.44 (1.08, 1.92)	<.0167
AE count during 1st week of intervention[c]	1	4.01 (2.78, 5.79)	<.0167	5.34 (3.18, 8.99)	<.0167	1.33 (0.76, 2.34)	.32
Any out of range blood pressures or heart rates during the experimental period[d,e]	1-20	0.68 (0.41, 1.13)	.14	1.09 (0.55, 2.16)	.81	1.60 (0.83, 3.10)	.16
Any carbon monoxide levels ≥ 50 ppm during the experimental period[e]	1-20	0.56 (0.33, 0.96)	.033	0.54 (0.29, 1.00)	.051	0.96 (0.55, 1.69)	.89
Any carbon monoxide levels ≥ 70 ppm during the experimental period[e]	1-20	0.49 (0.09, 2.70)	.42	0.49 (0.07, 3.52)	.48	1.00 (0.18, 5.50)	>.99

[a] *P*s<.0167 were considered significant for safety endpoints, note that non-significant p values do not indicate absence of differences ; Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249).

[b] Adverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).

[c] Negative binomial regression of total adverse event (AE) count (Definitely Related/Possibly Related/Relationship Unknown), adjusting for AE count at baseline (Week 0), with estimated incidence rate ratio (IRR) between groups being presented.

[d] Out of range blood pressure or heart rate was defined as either systolic ≥160 or <90 or diastolic ≥100 or <50 or heart rate ≥105 or <45 bpm.

[e] Logistic regression of any out of range events during Weeks 1-20, adjusting for any out of range events at baseline (Week 0), with estimated odds ratio (OR) between groups being presented.

Summary: Significantly greater numbers of adverse events were observed in the immediate versus gradual nicotine reduction and control groups and between gradual versus control group. The differences between the immediate compared to the other two groups occurred during the first week, but not thereafter (data not shown). No differences were observed across groups for out of range blood pressure, heart rate or CO levels. These results would indicate that more self-reported adverse events would likely be experienced with immediate reduction, but many of these events might be associated with withdrawal from nicotine (see eFigure 4). Other safety concerns were not evident.

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eTable 5. Number of Adverse Events[a,b]

			Post Randomization		
	Overall	**Baseline n=1250**	**Immediate n=503**	**Gradual n=498**	**Control n=249**
Total Number of Person-Weeks of Follow-up	-	-	7884	8812	4464
Total Number of Events	1182	15	570	435	162
Number of Events per Symptom					
Cough	229	4	105	90	30
Elevated CESD[c] Score	141	3	58	55	25
Headache, Non-migraine	76	0	31	36	9
Irritability (Frustration)	72	0	43	23	6
Sore/Itchy Throat	67	2	32	23	10
Increase in Phlegm	62	2	28	23	9
Nausea	40	0	23	13	4
Depressed (Sad) Mood	30	0	15	14	1
Dizziness/Lightheadedness	29	0	18	6	5
Nasal Congestion	25	1	11	7	6
Rhinorrhea (Runny Nose)	23	1	10	8	4
Shortness of Breath	23	0	7	12	4
Elevated Carbon Monoxide Level	21	1	6	9	5
Fatigue	20	0	12	3	5
Insomnia	20	0	9	7	4
Anxious (Nervous) Mood	18	0	13	4	1
Chest Congestion	17	0	8	6	3
Anger	15	0	13	2	0
Difficulty Concentrating	15	0	10	5	0
Chest Pain	13	0	6	4	3
Sleep Change/Disturbance, NOS[d]	13	0	8	4	1
Gastroesophageal Reflux Disease/Heartburn	11	0	7	3	1
Headache, Migraine	11	0	4	3	4
Abnormal Blood Test, NOS[d]	9	0	3	3	3
Loss of Appetite	9	0	6	2	1
Vivid Dreams	8	0	3	3	2
Vomiting	8	0	5	3	0
Dry Mouth	7	0	2	4	1
Hypertension	7	0	2	4	1
Increased Appetite/Hunger	7	0	2	3	2
Stress	7	0	4	2	1
Suicidal Ideation	7	0	4	2	1
Mouth Problem, NOS[d]	6	0	2	4	0
Restlessness	6	0	5	1	0
Wheezing	6	0	1	4	1
Numbness/Tingling/Neuropathy	5	0	2	3	0
Gastrointestinal Pain	5	0	3	2	0

			Post Randomization		
	Overall	Baseline n=1250	Immediate n=503	Gradual n=498	Control n=249
Sneezing	5	1	2	1	1
Weight Change	5	0	4	1	0
Constipation	5	0	4	1	0
Panic/Anxiety Attack	4	0	2	0	2
Change in Taste/Smell	4	0	2	1	1
Asthma	3	0	0	3	0
Bacterial Infection	3	0	2	0	1
Bronchitis	3	0	1	2	0
Diarrhea	3	0	1	1	1
Dyspepsia	3	0	2	1	0
Eye Problem/Infection	3	0	2	0	1
Nose/Throat Problem, NOS[d]	3	0	2	1	0
Rash	3	0	1	2	0
Skin Issue, NOS[d]	3	0	0	3	0
Bipolar Disorder	2	0	2	0	0
Bruxism	2	0	1	1	0
Drug Use Problem	2	0	2	0	0
Fainting	2	0	2	0	0
Mood Swings	2	0	2	0	0
Nightmare/Terror	2	0	0	1	1
Lung Pain	2	0	0	2	0
Musculoskeletal Pain	2	0	1	1	0
Changes in Saliva Production	2	0	2	0	0
Alcohol Use Problem	1	0	0	0	1
Allergies (Seasonal)	1	0	1	0	0
Binge Eating	1	0	0	1	0
Bloating	1	0	1	0	0
Chronic Obstructed Airway Disease	1	0	1	0	0
Dehydration	1	0	0	1	0
Dental/Teeth Problem	1	0	0	1	0
Depression, Clinical Diagnosis	1	0	0	1	0
Erectile Dysfunction	1	0	1	0	0
Excessive Sweating	1	0	1	0	0
Fever	1	0	0	1	0
Hair Loss	1	0	0	1	0
Hot Flashes	1	0	0	1	0
Kidney/Bladder/Urinary Problems, NOS[d]	1	0	1	0	0
Laryngitis	1	0	1	0	0
Lung ”Fullness”	1	0	0	1	0
Mania	1	0	0	1	0
Nasal/Sinus Drainage	1	0	0	1	0
Nosebleed/Dry Nasal Membrane	1	0	0	1	0

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			Post Randomization		
	Overall	Baseline n=1250	Immediate n=503	Gradual n=498	Control n=249
Pain at Phlebotomy Site	1	0	1	0	0
Fibromyalgia Pain	1	0	1	0	0
Sinus Pain	1	0	0	1	0
Pneumonia	1	0	0	1	0
Tachycardia	1	0	1	0	0
Tremors	1	0	1	0	0
Vertigo/Disequilibrium	1	0	1	0	0

[a]Events that were Definitely Related, Probably Related or Relationship Unknown were counted on a per symptom basis. Concurrent adverse events (e.g., cold symptoms) in the same participant would be counted as multiple events. Baseline refers only to events in participants who went on to be randomized.
[b]Adverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).
[c]Center for Epidemiological Studies Depression Scale
[d]Not Otherwise Specified

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eTable 6. Number of Participants with Adverse Events [a,b]

			Post Randomization		
	Overall	**Baseline n=1250**	**Immediate n=503**	**Gradual n=498**	**Control n=249**
Total Number of Person-Weeks of Follow-up	-	-	7884	8812	4464
Number of Participants with any Symptom	1056[c]	15	512	385	147
Number of Participants with Each Symptom					
Cough	196[c]	4	88	77	28
Elevated CESD[d] Score	110[c]	3	47	41	20
Irritability (Frustration)	68	0	40	22	6
Headache, Non-migraine	64	0	29	28	7
Sore/Itchy Throat	61	2	30	20	9
Increase in Phlegm	52[c]	2	24	20	7
Nausea	39	0	22	13	4
Depressed (Sad) Mood	29	0	15	13	1
Dizziness/Lightheadedness	27	0	17	5	5
Rhinorrhea (Runny Nose)	21	1	8	8	4
Insomnia	20	0	9	7	4
Nasal Congestion	20	1	8	7	4
Shortness of Breath	20	0	6	10	4
Fatigue	19	0	11	3	5
Anxious (Nervous) Mood	18	0	13	4	1
Elevated Carbon Monoxide Level	18	1	5	7	5
Chest Congestion	17	0	8	6	3
Difficulty Concentrating	15	0	10	5	0
Anger	14	0	12	2	0
Chest Pain	13	0	6	4	3
Sleep Change/Disturbance, NOS[e]	12	0	7	4	1
Gastroesophageal Reflux Disease/Heartburn	10	0	6	3	1
Abnormal Blood Test, NOS[e]	9	0	3	3	3
Headache, Migraine	9	0	3	3	3
Loss of Appetite	9	0	6	2	1
Vivid Dreams	8	0	3	3	2
Dry Mouth	7	0	2	4	1
Hypertension	7	0	2	4	1
Increased Appetite/Hunger	7	0	2	3	2
Stress	7	0	4	2	1
Suicidal Ideation	7	0	4	2	1
Vomiting	7	0	4	3	0
Mouth Problem, NOS[e]	6	0	2	4	0
Restlessness	6	0	5	1	0
Wheezing	6	0	1	4	1
Constipation	5	0	4	1	0
Numbness/Tingling/Neuropathy	5	0	2	3	0
Sneezing	5	1	2	1	1

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			Post Randomization		
	Overall	Baseline n=1250	Immediate n=503	Gradual n=498	Control n=249
Weight Change	5	0	4	1	0
Gastrointestinal Pain	4	0	2	2	0
Panic/Anxiety Attack	4	0	2	0	2
Bacterial Infection	3	0	2	0	1
Bronchitis	3	0	1	2	0
Diarrhea	3	0	1	1	1
Dyspepsia	3	0	2	1	0
Eye Problem/Infection	3	0	2	0	1
Nose/Throat Problem, NOS[e]	3	0	2	1	0
Rash	3	0	1	2	0
Skin Issue, NOS[e]	3	0	0	3	0
Change in Taste/Smell	3	0	1	1	1
Bruxism	2	0	1	1	0
Drug Use Problem	2	0	2	0	0
Fainting	2	0	2	0	0
Nightmare/Terror	2	0	0	1	1
Lung Pain	2	0	0	2	0
Musculoskeletal Pain	2	0	1	1	0
Changes in Saliva Production	2	0	2	0	0
Alcohol Use Problem	1	0	0	0	1
Allergies (Seasonal)	1	0	1	0	0
Asthma	1	0	0	1	0
Binge Eating	1	0	0	1	0
Bipolar Disorder	1	0	1	0	0
Bloating	1	0	1	0	0
Chronic Obstructed Airway Disease	1	0	1	0	0
Dehydration	1	0	0	1	0
Dental/Teeth Problem	1	0	0	1	0
Depression, Clinical Diagnosis	1	0	0	1	0
Erectile Dysfunction	1	0	1	0	0
Excessive Sweating	1	0	1	0	0
Fever	1	0	0	1	0
Hair Loss	1	0	0	1	0
Hot Flashes	1	0	0	1	0
Kidney/Bladder/Urinary Problems, NOS[e]	1	0	1	0	0
Laryngitis	1	0	1	0	0
Lung “Fullness”	1	0	0	1	0
Mania	1	0	0	1	0
Mood Swings	1	0	1	0	0
Nasal Sinus Drainage	1	0	0	1	0
Nosebleed/Dry Nasal Membrane	1	0	0	1	0
Pain at Phlebotomy Site	1	0	1	0	0

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			Post Randomization		
	Overall	**Baseline n=1250**	**Immediate n=503**	**Gradual n=498**	**Control n=249**
Fibromyalgia Pain	1	0	1	0	0
Sinus Pain	1	0	0	1	0
Pneumonia	1	0	0	1	0
Tachycardia	1	0	1	0	0
Tremors	1	0	1	0	0
Vertigo/Disequilibrium	1	0	1	0	0

[a]Events that were Definitely Related, Probably Related or Relationship Unknown were counted on a per participant basis. Baseline reflects randomized participants.
[b]Adverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).
[c] Symptom reported by same subject during baseline and post randomization.
[d]Center for Epidemiological Studies Depression Scale
[e]Not Otherwise Specified

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eTable 7. Count of Serious and Severe Adverse Events[a,b]

			Post Randomization			Follow-up		
	Overall	**Baseline n=1250**	**Immediate n=503**	**Gradual n=498**	**Control n=249**	**Immediate N=340**	**Gradual n=400**	**Control n=210**
Serious Adverse Events								
Number of serious adverse events (related/unrelated)	74	4	21	25	13	4	5	2
Number of serious adverse events (related, possibly related or unknown)	6	0	1	3	1	0	1[c]	0
Severe Adverse Events Including Serious Adverse Events								
Number of severe adverse events (related/unrelated)	317[d]	20	111	113	49	9	10	7
Number of severe adverse events (related, possibly related or unknown)	21	0	9	9	3	0	0	0

[a]Baseline reflects randomized participants.
[b]Adverse Events were ascertained by spontaneous report by the participant and assessed by investigators on health or medication changes, including CESD and respiratory symptoms, and on physiological measures (e.g., blood pressure, heart rate, carbon monoxide).
[c]Serious adverse event related to study procedure.
[d]Two participants reported the same symptom at baseline and post randomization.

Summary: Immediate reduction did not result in greater serious and/or severe adverse events, related and/or unrelated to study cigarettes, compared to gradual or control groups.

eTable 8. Serious Adverse Events (SAE): Related, Possibly Related and Unknown

#	Week	Seriousness	Relatedness	Event Description
SAE's Post Randomization – Immediate Group (N				
1	12	Hospitalization	**Unknown**	Surgery unknown etiology
SAE's Post Randomization – Gradual Group				
1	12	Hospitalization	**Possibly Related**	Pneumonia / lung infection
2	8	Hospitalization	**Possibly Related**	Asthma exacerbation
3	18	Hospitalization	**Possibly Related**	Flu-like symptoms and shortness of breath due to reactive airway disease
SAE's Post Randomization – Control Group				
1	18	Hospitalization	**Possibly Related**	Chest pain secondary to anxiety attack
SAE's During Follow-up – Gradual Group[c]				
1	Exit Visit (~Week 18)	Other Serious Intervention	**Related**	Seizure during breath holding for CO test

eTable 9. Non-Serious Severe and Related[a] Adverse Events

#	Week reported	Event
Immediate Group		
1	10	Depressed (sad) mood
2[b]	6, 8	Worsening of psychiatric symptoms
3[b]	8	Suicidal ideation
4	4	Drug use problem
5	4	Dizziness/Lightheadedness
6	1	Anxious (nervous) mood
7	1	Irritability
8	2	Elevated carbon monoxide level
Gradual Group		
1	2	Headache, Non-migraine
2[c]	8	Cough
3[c]	8	Increased phlegm
4[c]	8	Rhinitis (runny nose)
5[c]	8	Shortness of breath
6	4	Rash
Control Group		
1	18	Depressed (sad) mood
2	20	Cough

[a]Only includes Related, Possibly Related or Relationship Unknown.
[b]Same participant, multiple symptoms reported
[c]Same participant, multiple symptoms reported

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eTable 10. Participants Withdrawn, Post-Randomization, Due to Non-Serious Adverse Events

#	Week Withdrawn	Severity	Relatedness	Event description
Immediate Group – Subject Self Withdrawn				
1	2	Mild	**Related**	Withdrawal symptoms
2	3	Mild	**Possibly Related**	Cough, throat irritation
3	2	Mild	Remotely (Unlikely) Related	Muscle spasm
4	2	Severe	Unrelated	Traumatic injury
5	3	Severe	Remotely (Unlikely) Related	Kidney stones/pancreatitis
Immediate Group – PI Withdrawn due to AE				
1	2	Severe	**Related**	CO exceeded study safety standards
2	1	Mild	**Possibly Related**	Suicidal ideation (history of depressive symptoms)
3	1	Mild	**Possibly Related**	Suicidal ideation (history of depression)
Gradual Group – Subject Self Withdrawn				
1	2	Mild	**Related**	Headaches
2	6	Mild	**Possibly Related**	Racing thoughts and risk of relapse to drug use
3	6	Moderate	Remotely (Unlikely) Related	Sublingual growths
Gradual Group – PI Withdrawn due to AE				
1	8	Moderate	Unrelated	Unstable health
2	3	Mild	Unrelated	Untreated high blood pressure

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eTable 11. Characteristics of Week 20 Completers and Non-Completers

Characteristics	Completers (n = 958)	Non-Completers (n = 292)	Mean/Median Difference Completers vs. Non-Completers (95% CI)[c]	*P* Value
Age, mean (SD), years	46.1 (13.3)	41.7 (13.2)	4.4 (2.7, 6.1)	<.001
Median (IQR)	48.0 (35.0-56.0)	41.5 (30.0-52.5)	4.0 (3.0, 6.0)	
Female, No. (%)	441 (46)	108 (37)		.006
Race, No. (%)				.26
White	591 (63)	167 (59)		
Black	283 (30)	90 (32)		
Other	68 (7)	28 (10)		
Hispanic, No. (%)	38 (4)	28 (10)		<.001
Education, No. (%)				.43
< High school	78 (8)	19 (7)		
High school	305 (32)	103 (35)		
> High school	575 (60)	170 (58)		
Employment, No. (%)				.41
Employed (full and part-time)	423 (44)	137 (47)		
Unemployed	206 (22)	69 (24)		
Disability	104 (11)	24 (8)		
Other	225 (24)	62 (21)		
Cigarettes per day, mean (SD)	17.2 (8.6)	16.8 (8.4)	0.4 (-0.7, 1.6)	.44
Median (IQR)	15.8 (10.7-21.1)	15.1 (10.8-20.9)	0.4 (-0.6, 1.4)	
Years of regular smoking, mean (SD)	28.0 (13.5)	23.8 (13.5)	4.3 (2.5, 6.0)	<.001
Median (IQR)	29 (18-38)	23 (12-36)	4.0 (2.0, 6.0)	
Carbon monoxide, ppm, mean (SD)	19.1 (9.4)	19.3 (9.4)	-0.2 (-1.5, 1.0)	.68
Median (IQR)	17 (12-24)	18 (12-25)	0.0 (-1.0, 1.0)	
Total nicotine equivalents, nmol/mg creatinine, median (range)	62.9 (0.2 – 358.5)	58.6 (6.6 – 497.9)	4.3 (-0.0, 8.7)	.051
Nicotine metabolic ratio[a], mean (SD)	0.39 (0.24)	0.39 (0.23)	0.00 (-0.03, 0.04)	.82
Median (IQR)	0.35 (0.24-0.49)	0.35 (0.23-0.47)	-0.00 (-0.02, 0.03)	
FTND[b], mean (SD)	5.3 (2.1)	5.5 (2.1)	-0.2 (-0.5, 0.0)	.098
Median (IQR)	5 (4-7)	6 (4-7)	0 (-1, 0)	
Menthol cigarettes, No. (%)	437 (46)	148 (51)		.13
Other tobacco products, No. (%)	168 (21)	67 (28)		.018
Previous quit attempts for one day or longer, median (IQR)	2 (1-4)	2 (1-3)	0 (0, 0)	.20
Longest cigarette-free interval in days, median (IQR)	90 (14-365)	90 (14-365)	0 (-3, 13)	.52

[a]Nicotine metabolite ratio (free3'-hydroxycotinine:free cotinine) reflects the rate of nicotine metabolism. Compared to slow nicotine metabolism (plasma NMR <0.31), a fast nicotine metabolism (plasma NMR ≥ 0.31) is associated with increased smoking intensity and poorer smoking cessation.[13]

[b]Fagerström Test for Nicotine Dependence; scores range from 0 to 10 and higher scores indicate greater nicotine dependence

[c]The 95% CI of mean difference was calculated using Satterthwaite variance if folded F test of equality of variances was significant at p<0.05, otherwise, using pooled variance; Hodges-Lehmann estimate as the median of all paired differences between observations in the two samples was calculated together with asymptotic 95% CI.

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Summary: Completers were significantly older, more likely to be female, less likely to be Hispanic, had smoked for a longer duration and less likely to use other tobacco products.

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eTable 12. Biomarkers and Cigarettes per Day, Analysis of Measures at Week 20, by Different Missing Data Imputation Methods (Primary and Secondary Endpoints, Sensitivity Analyses)[a]

Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value
Measures at Week 20, Multiple Imputation[c], Unadjusted[d]						
CO (ppm)	-3.27 (-4.48, -2.07)	<.001	-5.31 (-6.77, -3.85)	<.001	-2.03 (-3.45, -0.61)	.005
3-HPMA (nmol/mg)	0.83 (0.74, 0.94)	.003	0.69 (0.60, 0.79)	<.001	0.83 (0.73, 0.95)	.005
PheT (pmolmgl)	0.90 (0.81, 0.99)	.034	0.78 (0.69, 0.87)	<.001	0.87 (0.78, 0.96)	.009
TNE (nmol/mg)	1.81 (1.41, 2.32)	<.001	0.21 (0.15, 0.28)	<.001	0.11 (0.09, 0.15)	<.001
Total NNAL (pmol/mg)	1.02 (0.86, 1.21)	.80	0.48 (0.39, 0.59)	<.001	0.47 (0.39, 0.57)	<.001
CEMA (nmol/mg)	0.60 (0.50, 0.71)	<.001	0.48 (0.40, 0.59)	<.001	0.81 (0.67, 0.97)	.022
HMPMA (nmol/mg)	0.84 (0.76, 0.94)	.002	0.68 (0.59, 0.77)	<.001	0.80 (0.70, 0.91)	<.001
SPMA (pmol/mg)	0.72 (0.61, 0.86)	<.001	0.61 (0.50, 0.73)	<.001	0.84 (0.69, 1.02)	.070
2-HPMA (nmol/mg)	0.91 (0.80, 1.04)	.16	0.76 (0.65, 0.88)	<.001	0.83 (0.72, 0.97)	.017
Cigarettes/day total	-6.40 (-7.54, -5.26)	<.001	-8.77 (-10.16, -7.37)	<.001	-2.37 (-3.75, -0.99)	<.001
Cigarettes/day study	-7.99 (-9.24, -6.75)	<.001	-10.62 (-12.14, -9.09)	<.001	-2.62 (-4.11, -1.14)	<.001
Cigarettes/day non-study	1.68 (0.99, 2.38)	<.001	1.86 (0.89, 2.83)	<.001	0.18 (-0.79, 1.14)	.72
Measures at Week 20, Last Observation Carried Forward Imputation[e], Unadjusted[d]						
CO (ppm)	-2.25 (-3.38, -1.13)	<.001	-4.09 (-5.48, -2.71)	<.001	-1.84 (-3.22, -0.45)	.009
3-HPMA (nmol/mg)	0.87 (0.79, 0.95)	.003	0.72 (0.64, 0.81)	<.001	0.83 (0.74, 0.93)	.001
PheT (pmol/ml\g)	0.93 (0.86, 1.01)	.086	0.83 (0.76, 0.92)	<.001	0.89 (0.81, 0.98)	.020
TNE (nmol/mg)	1.58 (1.27, 1.97)	<.001	0.25 (0.19, 0.33)	<.001	0.16 (0.12, 0.21)	<.001
Total NNAL (pmol/mg)	1.03 (0.90, 1.19)	.65	0.55 (0.46, 0.65)	<.001	0.53 (0.45, 0.63)	<.001
CEMA (nmol/mg)	0.66 (0.58, 0.75)	<.001	0.56 (0.48, 0.65)	<.001	0.84 (0.72, 0.99)	.036
HMPMA (nmol/mg)	0.86 (0.78, 0.94)	.001	0.68 (0.61, 0.77)	<.001	0.80 (0.71, 0.89)	<.001
SPMA (pmol/mg)	0.81 (0.71, 0.93)	.002	0.68 (0.58, 0.81)	<.001	0.84 (0.71, 0.99)	.042
2-HPMA (nmol/mg)	0.95 (0.86, 1.06)	.38	0.75 (0.66, 0.85)	<.001	0.79 (0.70, 0.89)	<.001
Cigarettes/day total	-5.43 (-6.57, -4.29)	<.001	-7.80 (-9.20, -6.39)	<.001	-2.37 (-3.77, -0.96)	.001
Cigarettes/day study	-7.13 (-8.27, -6.00)	<.001	-9.24 (-10.63, -7.85)	<.001	-2.11 (-3.50, -0.72)	.003
Cigarettes/day non-study	1.78 (1.03, 2.53)	<.001	1.52 (0.60, 2.45)	.001	-0.26 (-1.18, 0.67)	.59
Measures at Week 20, Baseline Imputation[f], Unadjusted[d]						
CO (ppm)	-2.48 (-3.47, -1.50)	<.001	-3.92 (-5.13, -2.72)	<.001	-1.44 (-2.65, -0.23)	.019
3-HPMA (nmol/mg)	0.90 (0.82, 0.98)	.017	0.76 (0.68, 0.85)	<.001	0.84 (0.76, 0.94)	.002
PheT (pmol/mg)	0.94 (0.87, 1.01)	.10	0.84 (0.76, 0.92)	<.001	0.89 (0.81, 0.97)	.012
TNE (nmol/mg)	1.71 (1.37, 2.13)	<.001	0.28 (0.21, 0.37)	<.001	0.16 (0.13, 0.22)	<.001
Total NNAL (pmol/mg)	1.06 (0.92, 1.21)	.43	0.58 (0.49, 0.68)	<.001	0.55 (0.46, 0.65)	<.001
CEMA (nmol/mg)	0.69 (0.61, 0.78)	<.001	0.58 (0.50, 0.68)	<.001	0.84 (0.72, 0.98)	.026
HMPMA (nmol/mg)	0.87 (0.80, 0.95)	.002	0.72 (0.64, 0.80)	<.001	0.82 (0.74, 0.92)	<.001

Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value
SPMA (pmol/mg)	0.83 (0.73, 0.94)	.004	0.73 (0.63, 0.86)	<.001	0.89 (0.76, 1.04)	.13
2-HPMA (nmol/mg)	0.95 (0.86, 1.04)	.28	0.82 (0.73, 0.92)	<.001	0.86 (0.77, 0.97)	.012
Cigarettes/day total	-4.36 (-5.27, -3.44)	<.001	-6.03 (-7.15, -4.91)	<.001	-1.67 (-2.79, -0.55)	.004
Measures at Week 20, Multiple Imputation[c], Adjusted[g]						
CO (ppm)	-3.40 (-4.61, -2.19)	<.001	-5.49 (-6.94, -4.04)	<.001	-2.09 (-3.50, -0.68)	.004
3-HPMA (nmol/mg)	0.82 (0.73, 0.92)	.001	0.68 (0.59, 0.77)	<.001	0.83 (0.73, 0.94)	.005
PheT (pmol/mg)	0.90 (0.81, 0.99)	.029	0.77 (0.69, 0.87)	<.001	0.86 (0.78, 0.96)	.006
TNE (nmol/mg)	1.78 (1.39, 2.27)	<.001	0.20 (0.15, 0.27)	<.001	0.11 (0.09, 0.15)	<.001
Total NNAL (pmol/mg)	1.00 (0.85, 1.19)	.99	0.46 (0.38, 0.57)	<.001	0.46 (0.38, 0.56)	<.001
CEMA (nmol/mg)	0.58 (0.49, 0.69)	<.001	0.47 (0.39, 0.57)	<.001	0.81 (0.68, 0.97)	.024
HMPMA (nmol/mg)	0.82 (0.74, 0.92)	<.001	0.66 (0.58, 0.75)	<.001	0.80 (0.71, 0.91)	.001
SPMA (pmol/mg)	0.71 (0.60, 0.84)	<.001	0.59 (0.49, 0.72)	<.001	0.83 (0.69, 1.01)	.063
2-HPMA (nmol/mg)	0.89 (0.78, 1.02)	.096	0.75 (0.65, 0.87)	<.001	0.84 (0.73, 0.98)	.026
Cigarettes/day total	-6.53 (-7.66, -5.40)	<.001	-8.78 (-10.16, -7.39)	<.001	-2.25 (-3.61, -0.88)	.001
Cigarettes/day study	-8.11 (-9.35, -6.87)	<.001	-10.62 (-12.13, -9.11)	<.001	-2.51 (-3.98, -1.04)	<.001
Cigarettes/day non-study	1.66 (0.96, 2.36)	<.001	1.85 (0.89, 2.82)	<.001	0.19 (-0.77, 1.15)	.69
Measures at Week 20, Last Observation Carried Forward Imputation[e], Adjusted[g]						
CO (ppm)	-2.49 (-3.63, -1.35)	<.001	-4.23 (-5.62, -2.83)	<.001	-1.74 (-3.14, -0.34)	.015
3-HPMA (nmol/mg)	0.85 (0.78, 0.93)	<.001	0.71 (0.63, 0.79)	<.001	0.83 (0.74, 0.93)	.002
PheT (pmol/mg)	0.94 (0.87, 1.01)	.097	0.83 (0.75, 0.91)	<.001	0.88 (0.80, 0.97)	.012
TNE (nmol/mg)	1.62 (1.30, 2.01)	<.001	0.25 (0.19, 0.32)	<.001	0.15 (0.12, 0.20)	<.001
Total NNAL (pmol/mg)	1.03 (0.89, 1.18)	.73	0.54 (0.45, 0.63)	<.001	0.52 (0.44, 0.62)	<.001
CEMA (nmol/mg)	0.63 (0.56, 0.72)	<.001	0.54 (0.46, 0.63)	<.001	0.85 (0.73, 1.00)	.052
HMPMA (nmol/mg)	0.84 (0.76, 0.92)	<.001	0.67 (0.60, 0.76)	<.001	0.80 (0.72, 0.90)	<.001
SPMA (pmol/mg)	0.79 (0.69, 0.91)	<.001	0.67 (0.57, 0.79)	<.001	0.85 (0.72, 1.00)	.052
2-HPMA (nmol/mg)	0.94 (0.85, 1.05)	.24	0.74 (0.65, 0.84)	<.001	0.78 (0.69, 0.89)	<.001
Cigarettes/day total	-5.56 (-6.72, -4.40)	<.001	-7.79 (-9.21, -6.37)	<.001	-2.23 (-3.66, -0.80)	.002
Cigarettes/day study	-7.34 (-8.49, -6.19)	<.001	-9.28 (-10.68, -7.88)	<.001	-1.94 (-3.34, -0.53)	.007
Cigarettes/day non-study	1.87 (1.09, 2.64)	<.001	1.58 (0.63, 2.52)	.001	-0.29 (-1.24, 0.66)	.55
Measures at Week 20, Baseline Imputation[f], Adjusted[g]						
CO (ppm)	-2.70 (-3.69, -1.71)	<.001	-4.11 (-5.32, -2.90)	<.001	-1.41 (-2.63, -0.19)	.024
3-HPMA (nmol/mg)	0.89 (0.81, 0.97)	.007	0.75 (0.67, 0.83)	<.001	0.84 (0.76, 0.94)	.002
PheT (pmol/mg)	0.94 (0.87, 1.01)	.11	0.83 (0.76, 0.91)	<.001	0.88 (0.80, 0.96)	.005
TNE (nmol/mg)	1.74 (1.40, 2.17)	<.001	0.28 (0.21, 0.36)	<.001	0.16 (0.12, 0.21)	<.001
Total NNAL (pmol/mg)	1.05 (0.92, 1.20)	.49	0.57 (0.48, 0.67)	<.001	0.54 (0.46, 0.64)	<.001
CEMA (nmol/mg)	0.66 (0.58, 0.75)	<.001	0.56 (0.48, 0.66)	<.001	0.85 (0.73, 0.99)	.041
HMPMA (nmol/mg)	0.85 (0.78, 0.93)	<.001	0.71 (0.64, 0.79)	<.001	0.83 (0.75, 0.93)	<.001
SPMA (pmol/mg)	0.80 (0.70, 0.90)	<.001	0.72 (0.61, 0.84)	<.001	0.90 (0.77, 1.05)	.19
2-HPMA (nmol/mg)	0.93 (0.85, 1.03)	.17	0.80 (0.72, 0.90)	<.001	0.86 (0.77, 0.97)	.013

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Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value
Cigarettes/day total	-4.45 (-5.38, -3.53)	<.001	-6.01 (-7.14, -4.89)	<.001	-1.56 (-2.69, -0.43)	.007
Change from Baseline at Week 20, Causal Effect[h]						
CO (ppm)	-6.23 (-10.8, -4.27)	.002	-8.21 (-12.68, -6.22)	<.001	-1.98 (-3.72, -0.30)	.014
3-HPMA (nmol/mg)	0.68 (0.50, 0.81)	.012	0.52 (0.37, 0.61)	<.001	0.76 (0.65, 0.88)	<.001
PheT (pmol/mg)	0.75 (0.66, 0.88)	.02	0.62 (0.54, 0.71)	<.001	0.83 (0.71, 0.94)	0.008
Total NNAL (pmol/mg)	0.49 (0.42, 0.80)	.014	0.17 (0.15, 0.24)	<.001	0.35 (0.25, 0.40)	<.001
CEMA (nmol/mg)	0.41 (0.33, 0.64)	.004	0.34 (0.27, 0.44)	<.001	0.82 (0.56, 0.98)	.026
HMPMA (nmol/mg)	0.65 (0.53, 0.76)	.002	0.49 (0.40, 0.58)	<.001	0.75 (0.64, 0.87)	<.001
SPMA (pmol/mg)	0.54 (0.42, 0.68)	<.001	0.46 (0.36, 0.57)	<.001	0.85 (0.70, 1.04)	.118
2-HPMA (nmol/mg)	0.80 (0.65, 1.00)	.052	0.70 (0.57, 0.85)	<.001	0.87 (0.71, 1.06)	.14
Cigarettes/day total	-6.97 (-8.92, -5.16)	<.001	-8.52 (-10.62, -6.89)	<.001	-1.55 (-2.81, -0.25)	.034

[a]CO, 3-HPMA, PheT are primary endpoints; TNE, total NNAL, CEMA, HMPMA, SPMA, 2-HPMA, and CPDs are secondary endpoints; all analyses in this table are sensitivity/secondary analyses (see Statistical Analysis Plan); see eTable 1 for the primary analysis results and p-value cutoffs for the primary analysis method. Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249); see Figure 2, eFigures 1 and 2 for the sample size at Week 20. See abbreviation glossary for name of acronyms.

[b]Mean difference in original scale for carbon monoxide (CO) and cigarettes/day and ratio of geometric means for the other outcomes; biomarkers are expressed as per mg creatinine.

[c]Missing values imputed with multiple imputation using the Markov Chain Monte Carlo (MCMC) method.

[d]Unadjusted: Linear regression unadjusted for any covariates except for the corresponding baseline measure; log-transformation was used for all the outcome variables and the corresponding baseline measures except for CO and cigarettes/day variables.

[e]Missing values imputed with the last observation carried forward (LOCF) method for dropouts and with trapezoidal rule for intermittent missing.

[f]Missing values imputed with baseline value for dropouts and with trapezoidal rule for intermittent missing.

[g]Adjusted: Linear regression adjusted for the corresponding baseline level of the outcome variable, study site, together with any baseline variables which were different between treatment arms at p<0.20 (employment, Fagerström Test for Nicotine Dependence, and serum nicotine metabolic ratio); log-transformation was used for the outcome variables and the corresponding baseline measures except for CO and cigarettes/day variables.

[h]The impact of adherence to only using study cigarettes was estimated using the compliance unsure reweighted estimator (CURE).[11] The causal effect refers to the effect that would have been observed if all participants were compelled to adhere with the protocol and smoke only study cigarettes. This is in contrast to the effect that is observed if analysis is completed using only the adherent subjects (i.e. the per protocol effect). Participants that adhere to the protocol are likely different that non-adherent participants on a number of covariates and, as a result, different than the original study population. Therefore, the population of adherent participants must be re-weighted to reflect the covariate distribution of the entire study population, which results in an estimate of the treatment effect that would have been observed had all subjects been adherent. The methodology used in this manuscript (the CURE estimator) is an extension of the inverse probability of compliance weighted estimator to the case where our measure of compliance is continuous and potentially measured with error (i.e. a biomarker). Outcomes were evaluated as the absolute change or percent reduction from baseline. Adherence in the immediate and gradual reduction groups was identified using total nicotine equivalents ($\leq$ 6 nmol/ml) at week 20.[12] Adherence could not be confirmed for participants lacking week 20 visit data and, therefore, participants that did not have data at week 20 were not included in the analysis. Participants in the control group were treated as compliant regardless of non-study cigarette use because control cigarettes have similar nicotine content to commercial cigarettes. Baseline covariates associated with adherence at week 20 and outcome at week 20 were identified using the LASSO with the tuning parameter identified by cross-validation and the final analysis adjusted for baseline covariates that were associated with both the outcome and adherence or that were associated with only the outcome. Confidence intervals and p-values were calculated using the non-parametric bootstrap.

Summary: At 20 weeks, lower toxicant exposures were observed in the immediate versus gradual nicotine reduction group (ranging from 16% to 40% based on MI, unadjusted) with the exception of total NNAL, 2-HPMA and possibly PheT, which showed less differences. An unexpected increase in TNE was observed in the immediate versus gradual group, which might be due to the higher rate of non-study cigarette use in the immediate reduction group. Differences remained between immediate versus control group on biomarkers of exposure, with lower exposures but higher mean non-study cigarette use in the immediate group. Lower exposures were observed for gradual versus control group on several of the outcome measures. In the causal effect analysis, which estimates the effects of study cigarettes taking into account non-adherence, the immediate reduction group experienced a range from 25% to 59% lower exposures than the gradual group on outcomes that showed significant differences in the primary analysis. These findings would suggest that even though a decrease in exposures are observed in the gradual nicotine reduction relative to the control group, there remains greater exposures in the gradual reduction versus immediate reduction group even after the gradual reduction group was switched to the 0.4 mg nicotine dose. A longer duration at the lower dose might be necessary in order to observe a substantial reduction in levels of toxicant exposure in the gradual nicotine reduction group.

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eTable 13. Analysis of Area Under the Curve and Measures at Week 20 for Primary Endpoints (CO, 3-HPMA, and PheT), by Using Random Site Effect Model (Primary Endpoints, Sensitivity Analysis)[a,b]

Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value
Area Under the Curve, Multiple Imputation[d], Unadjusted[e]						
CO (ppm)	-4.06 (-4.89, -3.23)	<.001	-3.38 (-4.40, -2.36)	<.001	0.68 (-0.31, 1.67)	.18
3-HPMA (nmol/mg)	0.83 (0.77, 0.88)	<.001	0.81 (0.75, 0.88)	<.001	0.98 (0.91, 1.06)	.64
PheT (pmol/mg)	0.88 (0.84, 0.93)	<.001	0.86 (0.84, 0.93)	<.001	0.98 (0.92, 1.04)	.51
Area Under the Curve, Last Observation Carried Forward Imputation[f], Unadjusted[e]						
CO (ppm)	-3.20 (-4.05, -2.34)	<.001	-2.74 (-3.79, -1.69)	<.001	0.46 (-0.59, 1.51)	.39
3-HPMA (nmol/mg)	0.84 (0.79, 0.89)	<.001	0.81 (0.76, 0.87)	<.001	0.96 (0.90, 1.04)	.32
PheT (pmol/mg)	0.90 (0.86, 0.95)	<.001	0.89 (0.84, 0.95)	<.001	0.98 (0.93, 1.05)	.61
Area Under the Curve, Baseline Imputation[g], Unadjusted[e]						
CO (ppm)	-3.48 (-4.19, -2.77)	<.001	-2.69 (-3.57, -1.82)	<.001	0.79 (-0.09, 1.66)	.077
3-HPMA (nmol/mg)	0.85 (0.81, 0.90)	<.001	0.84 (0.78, 0.89)	<.001	0.98 (0.92, 1.05)	.61
PheT (pmol/mg)	0.91 (0.87, 0.95)	<.001	0.89 (0.84, 0.94)	<.001	0.98 (0.93, 1.04)	.53
Area Under the Curve, Multiple Imputation[d], Adjusted[h]						
CO (ppm)	-4.23 (-5.05, -3.42)	<.001	-3.59 (-4.59, -2.59)	<.001	0.64 (-0.32, 1.61)	.19
3-HPMA (nmol/mg)	0.81 (0.76, 0.87)	<.001	0.80 (0.74, 0.86)	<.001	0.98 (0.91, 1.05)	.60
PheT (pmol/mg)	0.88 (0.83, 0.93)	<.001	0.86 (0.81, 0.92)	<.001	0.98 (0.92, 1.05)	.56
Area Under the Curve, Last Observation Carried Forward Imputation[f], Adjusted[h]						
CO (ppm)	-3.47 (-4.33, -2.61)	<.001	-2.96 (-4.00, -1.91)	<.001	0.51 (-0.54, 1.56)	.34
3-HPMA (nmol/mg)	0.82 (0.78, 0.87)	<.001	0.80 (0.75, 0.86)	<.001	0.97 (0.90, 1.04)	.38
PheT (pmol/mg)	0.90 (0.86, 0.95)	<.001	0.89 (0.84, 0.95)	<.001	0.99 (0.93, 1.05)	.69
Area Under the Curve, Baseline Imputation[g], Adjusted[h]						
CO (ppm)	-3.74 (-4.44, -3.03)	<.001	-2.94 (-3.81, -2.08)	<.001	0.79 (-0.08, 1.66)	.075
3-HPMA (nmol/mg)	0.84 (0.79, 0.88)	<.001	0.82 (0.77, 0.88)	<.001	0.98 (0.92, 1.05)	.61
PheT (pmol/mg)	0.90 (0.86, 0.95)	<.001	0.89 (0.84, 0.94)	<.001	0.98 (0.92, 1.04)	.55
Measures at Week 20, Multiple Imputation[d], Unadjusted[e]						
CO (ppm)	-3.27 (-4.48, -2.07)	<.001	-5.30 (-6.76, -3.84)	<.001	-2.03 (-3.45, -0.61)	.005
3-HPMA (nmol/mg)	0.83 (0.74, 0.94)	.003	0. 69 (0.60, 0.79)	<.001	0.83 (0.73, 0.95)	.005
PheT (pmol/mg)	0.90 (0.81, 0.99)	.033	0.78 (0.69, 0.87)	<.001	0.87 (0.78, 0.96)	.008
Measures at Week 20, Last Observation Carried Forward Imputation[f], Unadjusted[e]						
CO (ppm)	-2.25 (-3.38, -1.12)	<.001	-4.09 (-5.47, -2.71)	<.001	-1.84 (-3.22, -0.46)	.009
3-HPMA (nmol/mg)	0.87 (0.79, 0.95)	.003	0.72 (0.64, 0.81)	<.001	0.83 (0.74, 0.93)	.001
PheT (pmol/mg)	0.93 (0.87, 1.01)	.100	0.83 (0.75, 0.92)	<.001	0.88 (0.80, 0.97)	.012
Measures at Week 20, Baseline Imputation[g], Unadjusted[e]						
CO (ppm)	-2.48 (-3.46, -1.50)	<.001	-3.92 (-5.12, -2.72)	<.001	-1.44 (-2.64, -0.24)	.019
3-HPMA (nmol/mg)	0.90 (0.82, 0.98)	.017	0.76 (0.68, 0.84)	<.001	0.84 (0.76, 0.94)	.002
PheT (pmol/mg)	0.94 (0.87, 1.01)	.10	0.84 (0.77, 0.91)	<.001	0.89 (0.81, 0.97)	.010

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Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[c] (95% CI)	*P* Value
Measures at Week 20, Multiple Imputation[d], Adjusted[h]						
CO (ppm)	-3.41 (-4.62, -2.21)	<.001	-5.50 (-6.95, -4.05)	<.001	-2.08 (-3.49, -0.67)	.004
3-HPMA (nmol/mg)	0.82 (0.73, 0.92)	.001	0.68 (0.59, 0.77)	<.001	0.83 (0.73, 0.94)	.005
PheT (pmol/mg)	0.90 (0.81, 0.99)	.029	0.77 (0.69, 0.87)	<.001	0.86 (0.78, 0.96)	.006
Measures at Week 20, Last Observation Carried Forward Imputation[f], Adjusted[h]						
CO (ppm)	-2.49 (-3.64, -1.35)	<.001	-4.24 (-5.63, -2.84)	<.001	-1.74 (-3.15, -0.34)	.015
3-HPMA (nmol/mg)	0.85 (0.78, 0.93)	.001	0.71 (0.63, 0.80)	<.001	0.83 (0.74, 0.93)	.002
PheT (pmol/mg)	0.94 (0.87, 1.01)	.10	0.83 (0.75, 0.91)	<.001	0.88 (0.80, 0.97)	.011
Measures at Week 20, Baseline Imputation[g], Adjusted[h]						
CO (ppm)	-2.70 (-3.69, -1.71)	<.001	-4.11 (-5.32, -2.90)	<.001	-1.41 (-2.63, -0.19)	.024
3-HPMA (nmol/mg)	0.89 (0.81, 0.97)	.007	0.75 (0.67, 0.83)	<.001	0.84 (0.76, 0.94)	.002
PheT (pmol/mg)	0.94 (0.87, 1.01)	.11	0.83 (0.75, 0.90)	<.001	0.88 (0.80, 0.96)	.005

[a]CO, 3-HPMA, PheT are primary endpoints; all analyses in this table are sensitivity/secondary analyses (see Statistical Analysis Plan); see eTable 2 for the primary analysis results and p-value cutoffs for the primary analysis method. Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249), see Figure 2 for the sample size at each visit. See abbreviation glossary for name of acronyms.

[b]Area under the curve (AUC) scaled by time (i.e., time-scaled AUC); the unit is the same as its original variable; biomarkers are expressed as per mg creatinine.

[c]Mean difference in original scale for carbon monoxide (CO) and cigarettes/day and ratio of geometric means for the other outcomes

[d]Missing values imputed with multiple imputation using the Markov Chain Monte Carlo (MCMC) method.

[e]Unadjusted: Linear mixed model with a site random effect, unadjusted for any covariates except for the corresponding baseline measure; log-transformation was used for all the outcome variables and the corresponding baseline measures except for CO.

[f]Missing values imputed with the last observation carried forward (LOCF) method for dropouts and with trapezoidal rule for intermittent missing.

[g]Missing values imputed with baseline value for dropouts and with trapezoidal rule for intermittent missing.

[h]Adjusted: Linear mixed model with a site random effect, adjusted for the corresponding baseline level of the outcome variable and any baseline variables which were different between treatment arms at p<0.20 (employment, Fagerstrom Test for Nicotine Dependence, and serum nicotine metabolic ratio); log-transformation was used for the outcome variables and the corresponding baseline measures except for CO.

Summary: Linear mixed effects model for the 3 primary exposure variables (both AUC and Week 20 measure) were performed with site as a random effect, using different missing data imputation methods. The random site effect model and the linear regression model in eTables 1 and 12 gave almost identical results.

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eTable 14. Biomarkers and Cigarettes per Day for Each Four Week Period (Primary and Secondary Endpoints, Sensitivity Analyses)[a]

Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value
Linear Mixed Effects Model 1[c]							
CO (ppm)	4	-3.02 (-4.12, -1.92)	<.001	-2.39 (-3.72, -1.05)	<.001	0.63 (-0.67, 1.94)	.34
	8	-4.86 (-5.99, -3.73)	<.001	-3.27 (-4.63, -1.90)	<.001	1.60 (0.26, 2.93)	.019
	12	-6.76 (-7.91, -5.61)	<.001	-4.10 (-5.49, -2.72)	<.001	2.66 (1.31, 4.00)	<.001
	16	-5.52 (-6.68, -4.36)	<.001	-5.04 (-6.43, -3.65)	<.001	0.48 (-0.87, 1.84)	.49
	20	-3.74 (-4.91, -2.57)	<.001	-5.61 (-7.00, -4.21)	<.001	-1.87 (-3.23, -0.51)	.007
3-HPMA (nmol/mg)	4	0.85 (0.77, 0.93)	<.001	0.80 (0.71, 0.90)	<.001	0.94 (0.84, 1.05)	.29
	8	0.78 (0.71, 0.87)	<.001	0.76 (0.68, 0.86)	<.001	0.97 (0.87, 1.09)	.65
	12	0.70 (0.64, 0.78)	<.001	0.81 (0.72, 0.91)	<.001	1.15 (1.02, 1.30)	.019
	16	0.76 (0.69, 0.84)	<.001	0.76 (0.67, 0.86)	<.001	1.00 (0.89, 1.12)	.98
	20	0.83 (0.75, 0.92)	<.001	0.67 (0.59, 0.76)	<.001	0.81 (0.72, 0.91)	<.001
PheT (pmol/mg)	4	0.91 (0.84, 0.98)	.016	0.87 (0.80, 0.96)	.004	0.96 (0.88, 1.05)	.39
	8	0.85 (0.79, 0.92)	<.001	0.87 (0.79, 0.96)	.004	1.02 (0.93, 1.12)	.74
	12	0.83 (0.76, 0.90)	<.001	0.80 (0.73, 0.89)	<.001	0.97 (0.89, 1.07)	.59
	16	0.85 (0.78, 0.92)	<.001	0.83 (0.75, 0.92)	<.001	0.98 (0.89, 1.08)	.65
	20	0.90 (0.83, 0.97)	.010	0.77 (0.70, 0.85)	<.001	0.86 (0.78, 0.95)	.003
TNE (nmol/mg)	4	0.18 (0.15, 0.21)	<.001	0.18 (0.15, 0.23)	<.001	1.03 (0.83, 1.28)	.80
	8	0.20 (0.17, 0.24)	<.001	0.18 (0.14, 0.22)	<.001	0.89 (0.71, 1.11)	.29
	12	0.36 (0.30, 0.43)	<.001	0.18 (0.15, 0.23)	<.001	0.51 (0.41, 0.64)	<.001
	16	0.67 (0.55, 0.81)	<.001	0.17 (0.14, 0.22)	<.001	0.26 (0.21, 0.32)	<.001
	20	1.74 (1.44, 2.11)	<.001	0.19 (0.15, 0.24)	<.001	0.11 (0.09, 0.14)	<.001
Total NNAL (pmol/mg)	4	0.61 (0.54, 0.69)	<.001	0.64 (0.55, 0.74)	<.001	1.04 (0.90, 1.20)	.60
	8	0.54 (0.48, 0.61)	<.001	0.54 (0.47, 0.63)	<.001	1.01 (0.87, 1.17)	.93
	12	0.53 (0.47, 0.60)	<.001	0.48 (0.41, 0.56)	<.001	0.91 (0.79, 1.06)	.22
	16	0.72 (0.64, 0.82)	<.001	0.48 (0.41, 0.56)	<.001	0.66 (0.57, 0.76)	<.001
	20	0.97 (0.86, 1.10)	.64	0.45 (0.39, 0.53)	<.001	0.47 (0.40, 0.54)	<.001
CEMA (nmol/mg)	4	0.78 (0.69, 0.89)	<.001	0.78 (0.67, 0.91)	.001	1.01 (0.87, 1.16)	.91
	8	0.61 (0.54, 0.69)	<.001	0.64 (0.56, 0.75)	<.001	1.05 (0.91, 1.22)	.51
	12	0.48 (0.42, 0.54)	<.001	0.60 (0.52, 0.70)	<.001	1.26 (1.09, 1.46)	.002
	16	0.48 (0.43, 0.55)	<.001	0.54 (0.46, 0.63)	<.001	1.12 (0.96, 1.30)	.14
	20	0.59 (0.52, 0.67)	<.001	0.48 (0.41, 0.56)	<.001	0.781(0.69, 0.93)	.004
HMPMA (nmol/mg)	4	0.79 (0.72, 0.87)	<.001	0.77 (0.68, 0.86)	<.001	0.97 (0.87, 1.09)	.61
	8	0.74 (0.67, 0.82)	<.001	0.73 (0.64, 0.82)	<.001	0.98 (0.87, 1.10)	.73
	12	0.65 (0.59, 0.72)	<.001	0.73 (0.65, 0.82)	<.001	1.12 (0.99, 1.26)	.069
	16	0.76 (0.69, 0.85)	<.001	0.71 (0.63, 0.81)	<.001	0.93 (0.83, 1.05)	.26
	20	0.83 (0.75, 0.92)	<.001	0.64 (0.57, 0.73)	<.001	0.78 (0.69, 0.88)	<.001

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Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value
SPMA (pmol/mg)	4	0.78 (0.68, 0.89)	<.001	0.87 (0.74, 1.03)	.10	1.12 (0.95, 1.32)	.17
	8	0.70 (0.61, 0.80)	<.001	0.68 (0.58, 0.81)	<.001	0.98 (0.83, 1.15)	.78
	12	0.59 (0.51, 0.68)	<.001	0.73 (0.61, 0.86)	<.001	1.23 (1.04, 1.45)	.015
	16	0.62 (0.54, 0.72)	<.001	0.63 (0.53, 0.75)	<.001	1.02 (0.86, 1.20)	.86
	20	0.73 (0.63, 0.84)	<.001	0.61 (0.52, 0.73)	<.001	0.85 (0.71, 1.00)	.051
2-HPMA (nmol/mg)	4	0.90 (0.80, 1.00)	.047	0.83 (0.73, 0.94)	.005	0.92 (0.81, 1.05)	.23
	8	0.93 (0.83, 1.04)	.19	0.84 (0.73, 0.96)	.011	0.90 (0.79, 1.03)	.14
	12	0.82 (0.73, 0.92)	.001	0.89 (0.78, 1.02)	.10	1.08 (0.95, 1.24)	.26
	16	0.89 (0.79, 1.00)	.047	0.81 (0.70, 0.93)	.003	0.91 (0.79, 1.04)	.18
	20	0.89 (0.79, 1.01)	.066	0.73 (0.64, 0.84)	<.001	0.82 (0.72, 0.94)	.004
Cigarettes/day total	4	-1.93 (-2.84, -1.02)	<.001	-1.95 (-3.07, -0.83)	.001	-0.02 (-1.14, 1.10)	.97
	8	-5.37 (-6.30, -4.43)	<.001	-5.59 (-6.74, -4.45)	<.001	-0.23 (-1.36, 0.90)	.69
	12	-7.45 (-8.41, -6.50)	<.001	-6.93 (-8.09, -5.77)	<.001	0.52 (-0.62, 1.67)	.37
	16	-7.61 (-8.58, -6.65)	<.001	-7.68 (-8.85, -6.51)	<.001	-0.06 (-1.22, 1.09)	.91
	20	-6.20 (-7.17, -5.23)	<.001	-8.44 (-9.61, -7.27)	<.001	-2.24 (-3.40, -1.08)	<.001
Cigarettes/day study	4	-3.57 (-4.55, -2.60)	<.001	-3.56 (-4.76, -2.37)	<.001	0.01 (-1.19, 1.20)	.99
	8	-7.02 (-8.02, -6.02)	<.001	-6.80 (-8.02, -5.58)	<.001	0.22 (-0.99, 1.43)	.73
	12	-9.23 (-10.24, -8.21)	<.001	-8.42 (-9.65, -7.18)	<.001	0.81 (-0.41, 2.03)	.19
	16	-9.18 (-10.20, -8.16)	<.001	-9.35 (-10.60, -8.11)	<.001	-0.17 (-1.40, 1.05)	.78
	20	-7.86 (-8.88, -6.83)	<.001	-10.30 (-11.54, -9.05)	<.001	-2.44 (-3.67, -1.21)	<.001
Cigarettes/day non-study	4	1.64 (1.12, 2.16)	<.001	1.61 (0.97, 2.25)	<.001	-0.03 (-0.67, 0.61)	.92
	8	1.63 (1.09, 2.17)	<.001	1.18 (0.53, 1.83)	<.001	-0.45 (-1.10, 0.20)	.17
	12	1.74 (1.20, 2.29)	<.001	1.44 (0.78, 2.10)	<.001	-0.30 (-0.95, 0.35)	.37
	16	1.54 (0.99, 2.09)	<.001	1.64 (0.97, 2.31)	<.001	0.11 (-0.55, 0.76)	.75
	20	1.62 (1.07, 2.18)	<.001	1.82 (1.15, 2.49)	<.001	0.19 (-0.47, 0.85)	.57
Linear Mixed Effects Model 2[d]							
CO (ppm)	4	-3.09 (-4.19, -1.99)	<.001	-2.61 (-3.95, -1.28)	<.001	0.48 (-0.84, 1.79)	.48
	8	-4.75 (-5.87, -3.62)	<.001	-3.35 (-4.71, -1.99)	<.001	1.39 (0.06, 2.73)	.041
	12	-6.81 (-7.96, -5.67)	<.001	-4.39 (-5.76, -3.01)	<.001	2.43 (1.08, 3.77)	<.001
	16	-5.28 (-6.43, -4.12)	<.001	-4.99 (-6.37, -3.60)	<.001	0.29 (-1.06, 1.65)	.67
	20	-3.67 (-4.83, -2.51)	<.001	-5.70 (-7.09, -4.31)	<.001	-2.03 (-3.39, -0.68)	.003
3-HPMA (nmol/mg)	4	0.84 (0.76, 0.92)	<.001	0.79 (0.70, 0.88)	<.001	0.94 (0.84, 1.05)	.30
	8	0.77 (0.70, 0.85)	<.001	0.75 (0.66, 0.84)	<.001	0.97 (0.86, 1.09)	.60
	12	0.69 (0.62, 0.76)	<.001	0.79 (0.70, 0.89)	<.001	1.15 (1.02, 1.29)	.022
	16	0.76 (0.68, 0.84)	<.001	0.75 (0.66, 0.84)	<.001	0.99 (0.88, 1.11)	.81
	20	0.81 (0.73, 0.90)	<.001	0.65 (0.58, 0.74)	<.001	0.80 (0.71, 0.90)	<.001
PheT (pmol/mg)	4	0.90 (0.84, 0.98)	.011	0.87 (0.79, 0.96)	.004	0.96 (0.88, 1.06)	.43
	8	0.85 (0.79, 0.92)	<.001	0.87 (0.79, 0.96)	.004	1.02 (0.93, 1.12)	.73
	12	0.82 (0.76, 0.89)	<.001	0.80 (0.73, 0.88)	<.001	0.97 (0.88, 1.07)	.55

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Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value
	16	0.84 (0.78, 0.91)	<.001	0.82 (0.74, 0.91)	<.001	0.97 (0.89, 1.07)	.60
	20	0.90 (0.82, 0.97)	.008	0.77 (0.69, 0.85)	<.001	0.86 (0.78, 0.94)	.001
TNE (nmol/mg)	4	0.14 (0.15, 0.21)	<.001	0.18 (0.14, 0.22)	<.001	1.02 (0.82, 1.27)	.88
	8	0.20 (0.16, 0.24)	<.001	0.17 (0.14, 0.21)	<.001	0.87 (0.70, 1.09)	.23
	12	0.35 (0.29, 0.42)	<.001	0.18 (0.14, 0.22)	<.001	0.50 (0.40, 0.63)	<.001
	16	0.66 (0.55, 0.80)	<.001	0.17 (0.13, 0.21)	<.001	0.25 (0.20, 0.32)	<.001
	20	1.73 (1.43, 2.09)	<.001	0.18 (0.15, 0.23)	<.001	0.11 (0.09, 0.13)	<.001
Total NNAL (pmol/mg)	4	0.60 (0.53, 0.68)	<.001	0.62 (0.54, 0.72)	<.001	1.03 (0.90, 1.19)	.64
	8	0.53 (0.47, 0.60)	<.001	0.53 (0.45, 0.61)	<.001	1.00 (0.86, 1.15)	.98
	12	0.51 (0.45, 0.58)	<.001	0.47 (0.40, 0.54)	<.001	0.91 (0.78, 1.05)	.19
	16	0.71 (0.63, 0.81)	<.001	0.47 (0.40, 0.54)	<.001	0.65 (0.56, 0.76)	<.001
	20	0.95 (0.83, 1.07)	.40	0.44 (0.38, 0.51)	<.001	0.46 (0.40, 0.53)	<.001
CEMA (nmol/mg)	4	0.75 (0.66, 0.85)	<.001	0.76 (0.65, 0.88)	<.001	1.01 (0.87, 1.17)	.90
	8	0.60 (0.53, 0.67)	<.001	0.62 (0.53, 0.72)	<.001	1.04 (0.90, 1.20)	.61
	12	0.46 (0.41, 0.52)	<.001	0.58 (0.50, 0.67)	<.001	1.26 (1.08, 1.46)	.002
	16	0.47 (0.41, 0.53)	<.001	0.52 (0.45, 0.61)	<.001	1.11 (0.96, 1.29)	.15
	20	0.56 (0.50, 0.64)	<.001	0.46 (0.39, 0.53)	<.001	0.81 (0.70, 0.94)	.005
HMPMA (nmol/mg)	4	0.78 (0.70, 0.85)	<.001	0.76 (0.67, 0.85)	<.001	0.98 (0.87, 1.09)	.69
	8	0.73 (0.66, 0.80)	<.001	0.70 (0.62, 0.79)	<.001	0.97 (0.86, 1.09)	.56
	12	0.64 (0.57, 0.70)	<.001	0.70 (0.62, 0.79)	<.001	1.11 (0.99, 1.25)	.086
	16	0.75 (0.68, 0.83)	<.001	0.70 (0.62, 0.79)	<.001	0.93 (0.82, 1.04)	.21
	20	0.81 (0.73, 0.90)	<.001	0.63 (0.56, 0.71)	<.001	0.78 (0.69, 0.88)	<.001
SPMA (pmol/mg)	4	0.77 (0.67, 0.88)	<.001	0.86 (0.73, 1.01)	.066	1.12 (0.95, 1.32)	.17
	8	0.69 (0.60, 0.80)	<.001	0.66 (0.56, 0.78)	<.001	0.96 (0.81, 1.13)	.60
	12	0.58 (0.51, 0.67)	<.001	0.71 (0.60, 0.85)	<.001	1.22 (1.03, 1.44)	.019
	16	0.62 (0.53, 0.71)	<.001	0.62 (0.52, 0.74)	<.001	1.01 (0.85, 1.19)	.93
	20	0.69 (0.60, 0.80)	<.001	0.60 (0.50, 0.71)	<.001	0.86 (0.73, 1.02)	.084
2-HPMA (nmol/mg)	4	0.90 (0.81, 1.00)	.054	0.83 (0.73, 0.94)	.005	0.92 (0.81, 1.05)	.22
	8	0.92 (0.82, 1.03)	.16	0.83 (0.73, 0.95)	.008	0.90 (0.79, 1.03)	.12
	12	0.82 (0.73, 0.92)	<.001	0.88 (0.77, 1.01)	.078	1.08 (0.94, 1.23)	.27
	16	0.90 (0.80, 1.02)	.096	0.81 (0.70, 0.93)	.003	0.90 (0.78, 1.03)	.11
	20	0.88 (0.78, 1.00)	.043	0.72 (0.63, 0.83)	<.001	0.82 (0.71, 0.93)	.003
Cigarettes/day total	4	-2.08 (-3.01, -1.16)	<.001	-1.96 (-3.09, -0.83)	<.001	0.12 (-1.01, 1.25)	.83
	8	-5.54 (-6.49, -4.59)	<.001	-5.62 (-6.77, -4.46)	<.001	-0.08 (-1.22, 1.07)	.89
	12	-7.63 (-8.60, -6.67)	<.001	-6.94 (-8.11, -5.77)	<.001	0.70 (-0.46, 1.85)	.24
	16	-7.82 (-8.80, -6.85)	<.001	-7.72 (-8.90, -6.54)	<.001	0.10 (-1.07, 1.26)	.87
	20	-6.34 (-7.32, -5.36)	<.001	-8.47 (-9.65, -7.29)	<.001	-2.13 (-3.30, -0.96)	<.001
Cigarettes/day study	4	-3.77 (-4.75, -2.78)	<.001	-3.60 (-4.80, -2.40)	<.001	0.17 (-1.04, 1.38)	.78
	8	-7.24 (-8.25, -6.23)	<.001	-6.87 (-8.10, -5.65)	<.001	0.37 (-0.85, 1.59)	.55

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Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value	Mean Difference/Ratio of Geometric Means[b] (95% CI)	*P* Value
	12	-9.46 (-10.49, -8.44)	<.001	-8.46 (-9.70, -7.22)	<.001	1.00 (-0.23, 2.23)	.11
	16	-9.45 (-10.48, -8.41)	<.001	-9.45 (-10.70, -8.19)	<.001	0.00 (-1.24, 1.24)	>.99
	20	-8.09 (-9.13, -7.05)	<.001	-10.37 (-11.63, -9.12)	<.001	-2.29 (-3.53, -1.04)	<.001
Cigarettes/day non-study	4	1.68 (1.15, 2.22)	<.001	1.64 (0.98, 2.29)	<.001	-0.05 (-0.71, 0.61)	.88
	8	1.68 (1.13, 2.24)	<.001	1.24 (0.57, 1.91)	<.001	-0.45 (-1.11, 0.22)	.19
	12	1.80 (1.24, 2.37)	<.001	1.49 (0.81, 2.17)	<.001	-0.32 (-0.99, 0.36)	.36
	16	1.60 (1.03, 2.16)	<.001	1.69 (1.01, 2.38)	<.001	0.10 (-0.58, 0.77)	.78
	20	1.71 (1.14, 2.28)	<.001	1.87 (1.18, 2.56)	<.001	0.16 (-0.52, 0.84)	.65

[a]CO, 3-HPMA, PheT are primary endpoints; TNE, total NNAL, CEMA, HMPMA, SPMA, 2-HPMA, and CPDs are secondary endpoints; all analyses in this table are sensitivity/secondary analyses (see Statistical Analysis Plan); see eTable 2 for the primary analysis results and p-value cutoffs for the primary analysis method. Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249); see Figure 2, eFigures 1 and 2 for the sample size at each visit. See abbreviation glossary for name of acronyms.
[b]Mean difference in original scale for carbon monoxide (CO) and cigarettes/day (CPD); ratio of geometric means for the other outcomes; biomarkers are expressed as per mg creatinine.
[c]Linear mixed effects model 1: linear mixed model for repeated measures (CO and CPD in original scale, the others in log scale) with fixed effects of treatment, week, and treatment-week interaction, adjusting for corresponding (original-scale or log-transformed) baseline values (note: for CPD study, adjusting for the baseline value of CPD total); no imputation.
[d]Linear mixed effects model 2: linear mixed model for repeated measures (CO and CPD in original scale, the others in log scale) with fixed effects of treatment, week, and treatment-week interaction, adjusting for corresponding (original-scale or log-transformed) baseline values (note: for CPD study, adjusting for the baseline value of CPD total), study site, together with any baseline variables which were different between treatment arms at p<0.20 (employment, Fagerström Test for Nicotine Dependence, and serum nicotine metabolic ratio); no imputation.

Summary: General pattern of results from sensitivity analyses were consistent with primary analysis. Lower exposures at each 4-week period were observed in the immediate versus gradual nicotine reduction group, except for the following: no consistent differences were found for 2-HPMA, no differences were observed at Week 20 for total NNAL, and an increase in exposure was found at week 20 for TNE. Lower total and study cigarettes per day but higher r non-study cigarette use were observed in immediate versus gradual group. In general, lower exposures, total and study cigarettes per day but higher non-study cigarettes per day were observed in the immediate versus control group. For the gradual reduction versus control group, the results were less consistent, although lower levels were observed beginning at Week 12 for TNE and at Week 16 for total NNAL (due to the reduction in nicotine and NNK levels in the cigarettes). Higher concentrations of CO, CEMA and SPMA (Model 1 analysis) were observed at Week 12 for gradual versus control group, indicative of possible compensatory smoking behavior (e.g., smoking more intensely) at the 5.2 mg nicotine dose. These results confirm the primary analysis in which more rapid reduction in toxicant exposure in the immediate versus gradual reduction group and suggest possibly greater exposure in the gradual reduction group at moderate doses for a few of the biomarkers.

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eTable 15. Dependence Measures (Fagerström Test for Nicotine Dependence [FTND], Brief Wisconsin Inventory for Smoking Motives [WISDM]: Total, Primary and Secondary Dependence Motive Scores; Secondary Endpoint, Sensitivity Analysis) at Week 20[a]

Measures	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Multiple Imputation[d], Adjusted[e]						
FTND[b]	-1.02 (-1.30, -0.74)	<.001	-1.41 (-1.73, -1.10)	<.001	-0.39 (-0.71, -0.08)	.014
FTND without cigarettes per day (CPD)[b]	-0.65 (-0.87, -0.42)	<.001	-0.86 (-1.10, -0.61)	<.001	-0.21 (-0.44, 0.02)	.077
Brief WISDM total[c]	-3.01 (-4.63, -1.39)	<.001	-4.63 (-6.57, -2.70)	<.001	-1.63 (-3.32, 0.07)	.060
Brief WISDM primary [c]motives	-0.46 (-0.65, -0.28)	<.001	-0.68 (-0.90, -0.46)	<.001	-0.22 (-0.41, -0.02)	.028
Brief WISDM secondary motives[c]	-0.17 (-0.30, -0.03)	.021	-0.27 (-0.44, -0.10)	.002	-0.11 (-0.25, 0.04)	.16
Last Observation Carried Forward Imputation[f], Unadjusted[g]						
FTND[b]	-0.74 (-0.96, -0.52)	<.001	-1.10 (-1.38, -0.83)	<.001	-0.36 (-0.63, -0.09)	.009
FTND without CPD[b]	-0.42 (-0.59, -0.24)	<.001	-0.62 (-0.83, -0.41)	<.001	-0.20 (-0.41, 0.01)	.060
Brief WISDM total[c]	-1.45 (-2.76, -0.15)	.029	-2.53 (-4.13, -0.94)	.002	-1.08 (-2.68, 0.52)	.19
Brief WISDM primary[c]	-0.25 (-0.40, -0.11)	<.001	-0.42 (-0.60, -0.24)	<.001	-0.16 (-0.34, 0.02)	.073
Brief WISDM secondary[c]	-0.06 (-0.17, 0.05)	.30	-0.13 (-0.26, 0.01)	.078	-0.06 (-0.20, 0.07)	.36
Baseline Imputation[h], Unadjusted[g]						
FTND[b]	-0.52 (-0.72, -0.32)	<.001	-0.89 (-1.13, -0.64)	<.001	-0.37 (-0.62, -0.12)	.003
FTND without CPD[b]	-0.31 (-0.47, -0.15)	<.001	-0.49 (-0.68, -0.30)	<.001	-0.18 (-0.37, 0.01)	.066
Brief WISDM Total[c]	-0.38 (-1.57, 0.81)	.53	-0.96 (-2.42, 0.49)	.19	-0.58 (-2.04, 0.88)	.43
Brief WISDM Primary[c]	-0.11 (-0.24, 0.03)	.12	-0.23 (-0.40, -0.06)	.007	-0.12 (-0.29, 0.04)	.15
Brief WISDM Secondary[c]	0.01 (-0.10, 0.11)	.88	-0.01 (-0.13, 0.12)	.90	-0.02 (-0.14, 0.11)	.80
Last Observation Carried Forward Imputation[f], Adjusted[e]						
FTND[b]	-0.77 (-0.99, -0.55)	<.001	-1.06 (-1.34, -0.79)	<.001	-0.29 (-0.57, -0.02)	.036
FTND without CPD[b]	-0.44 (-0.62, -0.27)	<.001	-0.60 (-0.81, -0.39)	<.001	-0.16 (-0.37, 0.06)	.15
Brief WISDM Total[c]	-1.65 (-2.96, -0.35)	.013	-2.80 (-4.39, -1.21)	<.001	-1.14 (-2.75, 0.46)	.16
Brief WISDM Primary[c]	-0.29 (-0.44, -0.15)	<.001	-0.46 (-0.64, -0.28)	<.001	-0.17 (-0.35, 0.01)	.070
Brief WISDM Secondary[c]	-0.07 (-0.18, 0.05)	0.24	-0.14 (-0.28, 0.00)	.051	-0.07 (-0.21, 0.07)	.33
Baseline Imputation[h], Adjusted[e]						
FTND[b]	-0.53 (-0.73, -0.32)	<.001	-0.85 (-1.10, -0.60)	<.001	-0.32 (-0.57, -0.07)	.012
FTND without CPD[b]	-0.31 (-0.47, -0.15)	<.001	-0.47 (-0.66, -0.27)	<.001	-0.16 (-0.35, 0.04)	.12
Brief WISDM Total[c]	-0.46 (-1.66, 0.75)	.46	-1.17 (-2.64, 0.30)	.12	-0.71 (-2.19, 0.76)	.34
Brief WISDM Primary[c]	-0.13 (-0.27, 0.01)	.066	-0.26 (-0.43, -0.09)	.002	-0.13 (-0.30, 0.04)	.12
Brief WISDM Secondary[c]	0.01 (-0.10, 0.11)	.88	-0.02 (-0.15, 0.11)	.77	-0.03 (-0.16, 0.10)	.68

[a]FTND, FTND without cigarettes per day (CPD), Brief WISDM Total, Primary, and Secondary Dependence Motive Scores are secondary endpoints; all analyses in this table are sensitivity/secondary analyses (see Statistical Analysis Plan); see Table 2 for the primary analysis method results and *p*-value cutoff for the primary analysis method.

[b]Fagerstrom Test for Nicotine Dependence (FTND); sample sizes are Immediate (n=308), Gradual (n=389) and Control (n=207); FTND range of scores on scale from 0 to 10, with higher scores indicating greater nicotine dependence; FTND without CPD range of scores on scale from 0 to 7 with higher scores indicating greater nicotine dependence.

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[c]Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM): sample sizes are Immediate (n=308), Gradual (n=390) and Control (n=207);Total Score range from 11 to 77, with higher scores indicating greater smoking dependence; Primary Motives: Core features of dependence (Automaticity, Loss of Control, Craving, Tolerance), range of scores on scale 1 to 7; WISDM Secondary Motives: Instrumental motives for cigarette use (Affiliative Attachment, Cognitive Enhancement, Cue Exposure, Social Goads, Taste, Weight Control, and Affective Enhancement), range of scores on scale 1 to 7; for all WISDM scales, higher scores signify greater dependence motives.
[d]Missing values were imputed with multiple imputation using the Markov Chain Monte Carlo (MCMC) method.
[e]Adjusted: linear regression adjusted for the corresponding baseline level of the outcome variable, study site, together with any baseline variables which were different between treatment arms at $p<0.20$ (employment, FTND, and serum nicotine metabolite ratio).
[f]Missing values at week 20 were imputed with the last observation carried forward (LOCF) method.
[g]Unadjusted: linear regression unadjusted for any covariates except for the corresponding baseline measure.
[h]Missing values at week 20 were imputed with the baseline value.

Summary: Results from sensitivity analyses are consistent with primary analysis that showed lower scores on FTND with and without the cigarettes per day item and on WISDM Primary Dependence Motive score in immediate versus gradual nicotine reduction and versus control groups, with no consistent differences between gradual nicotine reduction versus control group.

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eTable 16. Dependence Measures (Fagerström Test for Nicotine Dependence [FTND], Brief Wisconsin Inventory for Smoking Motives [WISDM]: Total, Primary and Secondary Dependence Motive Scores) by Each 4-Week Period (Secondary Endpoints, Sensitivity Analysis)[a]

Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Linear Mixed Effects Model 1[b]							
FTND	4	-0.59 (-0.82, -0.37)	<.001	-0.68 (-0.96, -0.41)	<.001	-0.09 (-0.36, 0.17)	.49
	8	-1.02 (-1.25, -0.79)	<.001	-1.06 (-1.34, -0.78)	<.001	-0.04 (-0.31, 0.23)	.77
	12	-1.28 (-1.52,-1.05)	<.001	-1.33 (-1.61, -1.04)	<.001	-0.04 (-0.31, 0.23)	.76
	16	-1.26 (-1.49, -1.02)	<.001	-1.35 (-1.63, -1.06)	<.001	-0.09 (-0.36, 0.19)	.54
	20	-0.98 (-1.22, -0.74)	<.001	-1.43 (-1.71, -1.14)	<.001	-0.44 (-0.72, -0.17)	.002
FTND withoutCPD	4	-0.33 (-0.51, -0.15)	<.001	-0.37 (-0.58, -0.16)	<.001	-0.04 (-0.25, 0.17)	.70
	8	-0.58 (-0.76, -0.40)	<.001	-0.60 (-0.82, -0.39)	<.001	-0.03 (-0.24, 0.19)	.80
	12	-0.69 (-0.87, -0.51)	<.001	-0.77 (-0.99, -0.55)	<.001	-0.08 (-0.29, 0.14)	.48
	16	-0.65 (-0.84, -0.46)	<.001	-0.77 (-0.99, -0.55)	<.001	-0.12 (-0.34, 0.10)	.27
	20	-0.62 (-0.81, -0.44)	<.001	-0.86 (-1.08, -0.64)	<.001	-0.24 (-0.45, -0.02)	.034
Brief WISDM Total	4	-2.28 (-3.57, -0.99)	<.001	-1.64 (-3.20, -0.08)	.040	0.64 (-0.89, 2.17)	.41
	8	-3.16 (-4.48, -1.85)	<.001	-3.18 (-4.77, -1.58)	<.001	-0.01 (-1.56, 1.54)	.99
	12	-3.83 (-5.17, -2.49)	<.001	-3.30 (-4.91, -1.70)	<.001	0.53 (-1.03, 2.09)	.51
	16	-4.35 (-5.70, -3.00)	<.001	-4.34 (-5.96, -2.72)	<.001	0.01 (-1.56, 1.58)	.99
	20	-2.87 (-4.23, -1.51)	<.001	-4.16 (-5.78, -2.53)	<.001	-1.29 (-2.86, 0.29)	.11
Brief WISDM Primary[c]	4	-0.33 (-0.48, -0.19)	<.001	-0.28 (-0.46, -0.11)	.001	0.05 (-0.12, 0.22)	.57
	8	-0.49 (-0.64, -0.35)	<.001	-0.50 (-0.67, -0.32)	<.001	0.00 (-0.17, 0.17)	>.99
	12	-0.57 (-0.72, -0.42)	<.001	-0.47 (-0.65, -0.29)	<.001	0.10 (-0.07, 0.28)	.24
	16	-0.60 (-0.75, -0.45)	<.001	-0.59 (-0.77, -0.41)	<.001	0.01 (-0.17, 0.18)	.92
	20	-0.42 (-0.57, -0.27)	<.001	-0.63 (-0.81, -0.45)	<.001	-0.21 (-0.38, -0.03)	.019
Brief WISDM Secondary[c]	4	-0.13 (-0.25, -0.02)	.022	-0.08 (-0.22, 0.06)	.29	0.06 (-0.08, 0.20)	.40
	8	-0.17 (-0.29, -0.05)	.005	-0.17 (-0.32, -0.03)	.017	-0.01 (-0.14, 0.13)	.93
	12	-0.22 (-0.34, -0.10)	<.001	-0.21 (-0.35, -0.06)	.005	0.01 (-0.13, 0.15)	.87
	16	-0.28 (-0.40, -0.16)	<.001	-0.29 (-0.43, -0.14)	<.001	-0.01 (-0.15, 0.13)	.91
	20	-0.17 (-0.29, -0.05)	.007	-0.24 (-0.38, -0.09)	.001	-0.07 (-0.21, 0.07)	.34
Linear Mixed Effects Model 2[d]							
FTND	4	-0.61 (-0.84, -0.39)	<.001	-0.66 (-0.94, -0.39)	<.001	-0.05 (-0.32, 0.22)	.73
	8	-1.04 (-1.28, -0.81)	<.001	-1.05 (-1.33, -0.77)	<.001	0.00 (-0.28, 0.27)	.99
	12	-1.31 (-1.54, -1.07)	<.001	-1.30 (-1.58, -1.01)	<.001	0.01 (-0.27, 0.28)	.95
	16	-1.29 (-1.53, -1.05)	<.001	-1.34 (-1.62, -1.05)	<.001	-0.05 (-0.33, 0.23)	.73
	20	-1.00 (-1.24, -0.76)	<.001	-1.40 (-1.69, -1.11)	<.001	-0.40 (-0.68, -0.12)	.005
FTND without CPD	4	-0.35 (-0.53, -0.17)	<.001	-0.37 (-0.58, -0.15)	<.001	-0.02 (-0.23, 0.19)	.86
	8	-0.60 (-0.78, -0.42)	<.001	-0.62 (-0.84, -0.40)	<.001	-0.01 (-0.23, 0.20)	.89
	12	-0.71 (-0.89, -0.52)	<.001	-0.77 (-0.99, -0.55)	<.001	-0.06 (-0.28, 0.15)	.58

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Measures	Week	Immediate vs. Gradual		Immediate vs. Control		Gradual vs. Control	
		Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
	16	-0.69 (-0.87, -0.50)	<.001	-0.80 (-1.02, -0.57)	<.001	-0.11 (-0.33, 0.11)	.32
	20	-0.65 (-0.84, -0.46)	<.001	-0.86 (-1.09, -0.64)	<.001	-0.21 (-0.43, 0.00)	.053
Brief WISDM Total	4	-2.49 (-3.78, -1.20)	<.001	-1.89 (-3.45, -0.33)	.018	0.60 (-0.93, 2.13)	.44
	8	-3.36 (-4.68, -2.04)	<.001	-3.41 (-5.00, -1.81)	<.001	-0.04 (-1.60, 1.51)	.95
	12	-4.06 (-5.40, -2.72)	<.001	-3.58 (-5.19, -1.97)	<.001	0.48 (-1.08, 2.04)	.55
	16	-4.72 (-6.08, -3.37)	<.001	-4.67 (-6.29, -3.05)	<.001	0.06 (-1.52, 1.63)	.95
	20	-3.19 (-4.56, -1.83)	<.001	-4.52 (-6.15, -2.89)	<.001	-1.33 (-2.91, 0.25)	.098
Brief WISDM Primary[c]	4	-0.37 (-0.51, -0.23)	<.001	-0.32 (-0.49, -0.15)	<.001	0.05 (-0.12, 0.22)	.58
	8	-0.53 (-0.67, -0.38)	<.001	-0.54 (-0.71, -0.36)	<.001	-0.01 (-0.18, 0.16)	.93
	12	-0.61 (-0.76, -0.46)	<.001	-0.51 (-0.68, -0.33)	<.001	0.10 (-0.07, 0.27)	.24
	16	M-0.65 (-0.80, -0.50)	<.001	-0.63 (-0.81, -0.45)	<.001	0.01 (-0.16, 0.19)	.88
	20	-0.47 (-0.62, -0.32)	<.001	-0.68 (-0.86, -0.50)	<.001	-0.21 (-0.38, -0.03)	.020
Brief WISDM Secondary[c]	4	-0.14 (-0.26, -0.03)	.015	-0.09 (-0.23, 0.05)	.22	0.06 (-0.08, 0.19)	.42
	8	-0.18 (-0.30, -0.06)	.003	-0.18 (-0.32, -0.04)	.014	0.00 (-0.14, 0.14)	.96
	12	-0.23 (-0.35, -0.11)	<.001	-0.22 (-0.37, -0.08)	.002	0.01 (-0.13, 0.15)	.90
	16	-0.30 (-0.43, -0.18)	<.001	-0.31 (-0.45, -0.16)	<.001	0.00 (-0.14, 0.14)	.99
	20	-0.19 (-0.31, -0.06)	.003	-0.26 (-0.41, -0.11)	<.001	-0.07 (-0.22, 0.07)	.32

[a] FTND, FTND without CPD, WISDM Total, Primary, and Secondary Dependence Motive Scores are secondary endpoints. All analyses in this table are sensitivity/secondary analyses (see Statistical Analysis Plan); See Table 2 for the primary analysis method results and p-value cutoff for the primary analysis method. Immediate (randomized n=503), Gradual (randomized n=498), Control (randomized n=249), see Table 2 for the sample size at each visit. See abbreviation glossary for name of acronyms.

[b] Linear mixed effects model 1: linear mixed model for repeated measures with fixed effects of treatment, week, and treatment-week interaction, adjusting for corresponding baseline values; no imputation.

[c] WISDM Primary Dependence Motives: Core features of dependence (Automaticity, Loss of Control, Craving, Tolerance); WISDM Secondary Dependence Motives: Instrumental motives for cigarette use (Affiliative Attachment, Cognitive Enhancement, Cue Exposure/Associative Processes, Social/Environmental Goads, Taste, Weight Control, and Affective Enhancement).

[d] Linear mixed effects model 2: linear mixed model for repeated measures with fixed effects of treatment, week, and treatment-week interaction, adjusting for corresponding baseline values, study site, together with any baseline variables which were different between treatment arms at p<0.20 (employment, Fagerström Test for Nicotine Dependence, and serum nicotine metabolic ratio); no imputation.

Summary: Results from sensitivity analyses are consistent with the primary analysis results and suggest a more rapid reduction in cigarette dependence with immediate nicotine reduction compared to gradual nicotine reduction, with minimal differences between gradual nicotine reduction versus control group.

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