A RANDOMIZED, CONTROLLED, SIX-WAY CROSSOVER CLINICAL STUDY TO CHARACTERIZE THE NICOTINE PHARMACOKINETICS AND SUBJECTIVE EFFECTS OF FOUR HEATED TOBACCO PRODUCTS IN ADULT MENTHOL AND NON- MENTHOL CIGARETTE SMOKERS

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CLINICAL STUDY PROTOCOL

A RANDOMIZED, CONTROLLED, SIX-WAY CROSSOVER CLINICAL STUDY TO CHARACTERIZE THE NICOTINE PHARMACOKINETICS AND SUBJECTIVE EFFECTS OF FOUR HEATED TOBACCO PRODUCTS IN ADULT MENTHOL AND NON-MENTHOL CIGARETTE SMOKERS

Altria Client Services LLC Study No.: ALCS-REG-23-08-HT (Ploom® PK)
Contract Research Organization Project No.: CA41312

Version: 1.0

Protocol Date: 19-Oct-2023

Sponsor: Altria Client Services LLC
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SIGNATURES

SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE
Altria Client Services LLC Study No.: ALCS-REG-23-08-HT (Ploom® PK)

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I have read the following protocol and agreed to the conduct of the study as described herein:

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INVESTIGATOR AGREEMENT AND SIGNATURE PAGE
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A RANDOMIZED, CONTROLLED, SIX-WAY CROSSOVER CLINICAL STUDY TO CHARACTERIZE THE NICOTINE PHARMACOKINETICS AND SUBJECTIVE EFFECTS OF FOUR HEATED TOBACCO PRODUCTS IN ADULT MENTHOL AND NON-MENTHOL CIGARETTE SMOKERS

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Altria Client Services LLC prior to seeking approval from the Institutional Review Board (IRB).

This study will be conducted in accordance with Good Clinical Practice (GCP) based on the current International Council for Harmonisation (ICH) guidelines for GCP and the corresponding sections of the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Participants (Title 21 CFR Part 50), IRBs (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Printed Name:
	(Signature) Date

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STUDY OUTLINE

Protocol Title	A randomized, controlled, six-way crossover clinical study to characterize the nicotine pharmacokinetics and subjective effects of four heated tobacco products in adult menthol and non-menthol cigarette smokers
Brief Title	Pharmacokinetic and abuse liability characterization of heated tobacco products against combustible cigarette and nicotine gum in confinement
Purpose	The purpose of this study is to characterize the plasma nicotine pharmacokinetic (PK) parameters, and subjective effects of four Ploom® heated tobacco products (HTPs) (two menthol and two tobacco flavor heated tobacco stick (HTS) varieties relative to participant's usual brand combustible cigarette (UBCC) and nicotine gum (a nicotine replacement therapy [NRT]) in adult menthol and non-menthol combustible cigarette smokers. The results of this study will allow assessment of nicotine PK and abuse liability (AL) of the HTPs compared to UBCC and nicotine gum as a high and low AL reference products, respectively.
Objectives	*Main Objectives:* • Characterize PK parameters of nicotine in plasma during and after a single *ad libitum* use of HTP (two menthol and two tobacco flavor varieties) relative to UBCC and the nicotine gum. • Characterize Product Liking of HTP (two menthol and two tobacco flavor varieties) during and after a single *ad libitum* use relative to UBCC and the nicotine gum. • Characterize additional subjective measures of HTP (two menthol and two tobacco flavor varieties) during and after a single *ad libitum* use relative to UBCC and the nicotine gum. • Assess heart rate following the use of HTP (two menthol and two tobacco flavor varieties) relative to UBCC and the nicotine gum. • Characterize product use of HTP during a single *ad libitum* use. • Assess safety profiles of HTP (two menthol and two tobacco flavor varieties) compared to UBCC and nicotine gum with monitoring of adverse experiences, symptom-driven physical examinations, and relevant clinical laboratories as needed. *Exploratory Objectives:* • Characterize N-nitrosonornicotine (NNN) uptake and compare the difference during HTP and UBCC use. • Assess additional Product Liking parameters during each morning *ad libitum* product use.

Endpoints	*Main Endpoints:*
	• Baseline-adjusted plasma nicotine PK parameters following a single *ad libitum* HTP, UBCC, or nicotine gum use:
	  • C_{max}: Maximum measured plasma concentration.
	  • $AUC_{(0\text{-}180)}$: Area under the nicotine concentration-time curve calculated using linear trapezoidal summation from time zero (defined as the start of product use) to 180 minutes.
	  • T_{max}: Time of the maximum measured plasma concentration.
	• Assessment of Product Liking during and following the morning *ad libitum* product use PK test session:
	  • Original scores
	  • $E_{max\text{-}PL}$: Maximum product liking in visual analogue scale (VAS) score during each morning *ad libitum* product use.
	• Subjective Effects (questionnaires scores during and following the morning *ad libitum* product use PK test session):
	  • Tobacco/Nicotine Withdrawal Questionnaire
	  • Original scores
	  • $E_{max\text{-}TNW}$: For response to Tobacco/Nicotine Withdrawal scales, the maximum reduction in VAS score from baseline pre-use to post-use (i.e., $VAS_{pre\text{-}use} - VAS_{post\text{-}use}$) for each morning *ad libitum* product use.
	  • Direct Effects of Product Questionnaire
	  • Original scores
	  • $E_{max\text{-}DEP}$: For response to Direct Effects of Product, the largest VAS score recorded for each morning *ad libitum* product use.
	  • Use the Product Again Questionnaire
	  • Original scores
	  • Bipolar scores
	  • Modified Cigarette Evaluation Questionnaire (mCEQ)
	  • Original scores
	  • Factor scores
	• Physiological heart rate assessments measured during morning *ad libitum* product use PK test session

	• Product Use
	  • Number of HTS, UBCC, and nicotine gum used in the afternoon product use session
	  • Puff count during the morning *ad libitum* product use PK test sessions for UBCC and HTP products
	• Safety
	  • Physical examination (symptom driven) findings
	  • Results of adverse experience (AE) monitoring
	  • Clinical laboratory findings, as applicable
	Exploratory Endpoints:
	• Plasma NNN levels following HTP and UBCC use
	  • Maximum change from baseline for plasma NNN levels
	• Assessment of Product Liking parameter over 180 minutes
	  • $AUEC_{PL}$: Area under the effect curve for product liking during each morning *ad libitum* product use.

Study Design	This is a randomized, controlled, six-way crossover clinical study to characterize the nicotine PK and subjective effects of HTPs (2 menthol varieties, Products A and B; 2 tobacco flavor varieties, Products C and D) in adult menthol and non-menthol combustible cigarette smokers. The study will include participants' UBCC (Product F) and a nicotine gum (Product E) as high and low abuse liability reference products, respectively, to the HTP. Results of this study will help in determining abuse liability of HTP products in current smokers. **Study Events and Procedures** *Screening* Screening will occur within 28 days prior to Day 1 and includes administering the Fagerström Test for Cigarette Dependence (FTCD), standard safety procedures, collection of baseline information, and a 5-day at-home HTP product trial period. *Enrollment Visit & At-home Product Trial* Enrollment visit (Day -6) will occur 5 days prior to Check-in (Day -1). Participants will receive all four varieties of HTS on Day -6 and begin the at-home product trial. Participants are required to use each HTS variety at least once a day *ad libitum* for a minimum of 20 HTS uses over 5 days. *Check-in (Day -1) & Randomization* Participants will check-in on the morning of Day -1. Participants will be randomized based on sex and their UBCC (menthol or non-menthol) to

	one of six product use sequences. Once participants are randomized to a product use sequence, product use sessions in confinement will start. Participants will remain in confinement at the clinic until completion of all study activities on Day 6. *Day -1 to Day 6* Starting on Day -1 (following Check-in) through Day 5, depending on the randomized product use sequence, participants will use their assigned product (HTP, UBCC, or nicotine gum) during an afternoon product use session. Participants will use the same assigned product to be tested during the next day's morning *ad libitum* product use PK test session (e.g., if a participant is assigned to Product A [HTP] as the product to be used in the morning *ad libitum* product use PK test session on Day 1, the participant will use Product A [HTP] during the afternoon product use session on Day -1). The afternoon product use session should be no more than approximately 6 hours long. Participants will be required to use the assigned study product at least once, but no more than six HTS, UBCC, or nicotine gum *ad libitum* per daily afternoon product use sessions. Participants will then be required to abstain from any tobacco- or nicotine-containing products for at least 12 hours prior to the start of the following morning's *ad libitum* product use PK test session. Morning *ad libitum* product use PK test sessions will occur on the mornings of Days 1, 2, 3, 4, 5, and 6 (for a total of 6 morning *ad libitum* product use PK test sessions). During the morning *ad libitum* product use PK test session, participants will use the assigned study product per their assigned product use sequence. Participants will use a single UBCC or HTP for 5 minutes *ad libitum* or use the nicotine gum for 30 minutes per product use instruction. Blood samples for PK will be collected prior to and for 3 hours following the start of each morning *ad libitum* product use PK test session. Heart rate measurements will be taken at specified time points during each morning *ad libitum* product use PK test session. In addition, participants will complete subjective effects questionnaires (Product Liking, Tobacco/Nicotine Withdrawal, Direct Effects of Product, Use Product Again, and mCEQ) at designated time points during each morning *ad libitum* product use PK test session.
Study Population and Sample Size	Participants will be generally healthy adult male and female combustible cigarette smokers between 22 and 65 years of age, inclusive, determined at screening. Participants must be current menthol or non-menthol combustible cigarette smokers with self-reported cigarette smoking history of at least 12 months prior to screening and have a history of smoking ≥ 10 to ≤ 30 combustible cigarettes per day. The study will recruit approximately 60 adult cigarette smokers (composed of approximately 30 menthol and 30 non-menthol adult

<table>
<tr><td></td><td colspan="3">smokers) with the goal of obtaining approximately 48 completed participants (approximately 24 menthol and 24 non-menthol smokers). Every attempt will be made to enroll no less than 40% of either sex for menthol and non-menthol smokers, respectively.</td></tr>
<tr><td>Study Products and Route of Administration</td><td>Product</td><td>Description</td><td>Route of Administration</td></tr>
<tr><td></td><td>A</td><td>Ploom® 3.1 HTP - Menthol HTS; MX3 (681)
(Test Product)</td><td>Inhalation</td></tr>
<tr><td></td><td>B</td><td>Ploom® 3.1 HTP - Menthol HTS; MX5 (706)
(Test Product)</td><td>Inhalation</td></tr>
<tr><td></td><td>C</td><td>Ploom® 3.1 HTP - Tobacco HTS; R8 (120)
(Test Product)</td><td>Inhalation</td></tr>
<tr><td></td><td>D</td><td>Ploom® 3.1 HTP - Tobacco HTS; RX4 (953)
(Test Product)</td><td>Inhalation</td></tr>
<tr><td></td><td>E</td><td>Nicorette® 4 mg Mint Nicotine Gum
(Reference Product)</td><td>Oral</td></tr>
<tr><td></td><td>F</td><td>Combustible Cigarette (menthol or non-menthol), participant’s usual brand
(Reference Product)</td><td>Inhalation</td></tr>
<tr><td>Statistical Analysis</td><td colspan="3">Pharmacokinetic Analysis

A linear mixed model for analysis of variance will be performed on the natural log-transformed PK parameters C_{max} and $AUC_{(0-180)}$ for nicotine to compare each HTP to the reference products, UBCC and nicotine gum (NRT), respectively. The model will include sequence, study product, and study day as fixed effects and participant-nested-within-sequence as a random effect. Sequence will be tested using participant-nested-within-sequence as the error term. Geometric least squares means (LSM) and 90% confidence intervals (CIs) will be provided for the PK parameters of C_{max} and $AUC_{(0-180)}$ by study product. Geometric LSM ratio, 90% CIs of geometric LSM ratio, and p-values will be provided for the study product comparisons among each of HTP products and the reference products (UBCC and gum [NRT], respectively) in C_{max} and $AUC_{(0-180)}$. The above statistical analyses will be performed using the appropriate SAS procedure. Descriptive statistics will be provided as appropriate.

Subjective Measures

Analysis will be performed for data from the 5 questionnaires (Product Liking; Tobacco/Nicotine Withdrawal; Direct Effects of Product; Use Product Again; mCEQ). Descriptive statistics will be provided. Analysis, where applicable, will include use of a linear mixed model for maximum subjective effect score (E_{max}).</td></tr>
</table>

	Physiological Heart Rate Assessments Descriptive statistics will be performed for physiological heart rate data collected during morning *ad libitum* product use PK test sessions. *Safety Analysis* Adverse experiences (AEs) will be summarized by product. Safety data will be summarized by time point of collection as appropriate and for available data. Descriptive statistics will be calculated for quantitative and frequency counts will be compiled for classification of qualitative safety data as appropriate. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

SUMMARY OF EVENTS

Table 1: Overall Summary of Events

Study Procedure	Screening		Study Days (Confinement)						
Study Days →	- 28 to -7	-6 to -2 (At-home Product Trial)	-1	1	2	3	4	5	6 (EOS/ET [a])
Inclusion/exclusion criteria	X		X [b]						
Verified Clinical Trials Consent	X								
Informed consent	X								
Demographics	X								
Medical, surgical, tobacco/nicotine use history	X		X [b]						
Concomitant medications	X	X	X	X	X	X	X	X	X
FTCD	X								
Height, body weight, BMI [c]	X								
Physical examination	X								
Symptom-driven physical examination		X (at the discretion of the Investigator)							
Adverse experience assessment		X	X	X	X	X	X	X	X
Vital signs (BP, HR, RR, oral temperature) [d]	X		X						X
12-lead ECG [e]	X								
Clinical Labs (Hem, Chem, and UA)	X								
Serology (HIV, Hep B, and Hep C)	X								
Serum pregnancy test (all females) [f]	X								
Urine/serum pregnancy test (all females) [f]			X						X
FSH (post-menopausal or symptomatic females only)	X								
Urine drugs of abuse and urine/breath alcohol screen	X		X						
Cotinine screen (urinary)	X								
Exhaled carbon monoxide	X								
At-home product acclimation [g]		X							
Product use sequence randomization			X						
Check-in			X						
Confinement at the site			X	X	X	X	X	X	X
Questionnaire training [h]			X						
Product use training [i]		X	X						
Daily afternoon product use sessions [j]			X	X	X	X	X	X	

Study Procedure	Screening		Study Days (Confinement)						
Study Days →	- 28 to -7	-6 to -2 (At-home Product Trial)	-1	1	2	3	4	5	6 (EOS/ET [a])
12- hour tobacco/ nicotine product abstention [k]			X	X	X	X	X	X	
Morning *ad libitum* product use PK test session [l]				X	X	X	X	X	X
Blood collection for PK [m]				X	X	X	X	X	X
Physiological HR assessments [n]				X	X	X	X	X	X
Subjective effects questionnaires [o]				X	X	X	X	X	X
Product use compliance assessment [p]			X	X	X	X	X	X	X

Abbreviations: BP = blood pressure; BMI = body mass index; Chem = serum chemistry; ECG = electrocardiogram; EOS = end-of-study; ET = early termination; FSH = follicle-stimulating hormone; FTCD = Fagerström Test for Cigarette Dependence; Hem = hematology; Hep B = hepatitis B; Hep C = hepatitis C; HIV = human immunodeficiency virus; HR = heart rate; HTP = heated tobacco product; HTS = heated tobacco stick; NRT = nicotine replacement therapy; PK = pharmacokinetic(s); RR = respiratory rate; UA = urinalysis.

a. Participants who withdraw from the study early will have end of study procedures performed at the time of discontinuation.
b. Assessments conducted on Day -1 will be used to reconfirm a participant's eligibility for continuation in the study and to determine if any changes have occurred since screening.
c. The BMI will be calculated in the electronic data capture system using the height and weight obtained at screening.
d. Blood pressure and heart rate will be measured after the participant has been resting quietly in a seated position for at least 10 minutes.
e. The 12-lead ECGs will be performed after the participant has been resting quietly in a supine position or in the most recumbent position possible for at least 5 minutes.
f. Serum pregnancy test will be performed for all females at screening. At Check-in and at end of study or early termination, urine/serum pregnancy tests will be performed to document no-pregnancy occurred.
g. At-home product acclimation will last for 5 days (Day -6 through Day -2) prior to check on Day -1, participants will be given an HTP device and sufficient HTSs to allow participants to acclimate to the products.
h. Questionnaire training will occur at Check-in to ensure participant understands how to complete visual analogue scales on an electronic patient reported outcome device prior to the morning *ad libitum* product use PK test session. Participants will also be trained on a paper version of the questionnaires as a backup in case of computer issues during the study.
i. Prior to sending participants home with the study HTP products on Day -6, participants must be instructed on the proper operation of the HTP device and how to insert/remove the HTS. Participants should receive instructions on how to use the NRT (gum) on Day -1 to ensure all participants know the proper use of the gum. Participants will not be provided any gum for the at-home product trial.
j. Daily afternoon product use sessions will occur during study conduct in confinement; participants will use an assigned test product scheduled to be used during the next day's morning *ad libitum* product use PK test session.

k. All participants will abstain from tobacco/nicotine-containing products for at least 12 hours prior to the start of the morning *ad libitum* product use PK test session scheduled on the following day.
l. PK test session will start in the morning, where participants will use the assigned study product (reference and test products) *ad libitum* for a given amount of time. There will be blood collection, HR measurements, and subjective effects assessments at designated nominal time points as listed in Table 2**.** In addition, site staff will record puff counts on days when UBCC or Ploom® HTP are used.
m. At designated time points during the morning *ad libitum* product use PK test sessions only. See Table 2 for the scheduled time points.
n. Physiological HR assessments will be assessed at designated time points during the morning *ad libitum* product use PK test sessions. See Table 2 for the scheduled time points. Heart rate measurements will be performed prior to the blood draw (approximately 1 minute prior to the scheduled blood draw time point) when scheduled at the same time.
o. Subjective effects will be captured via questionnaires (refer to the Appendices Appendix for a list of questionnaires to be assessed), at designated nominal time points. See Table 2 for the scheduled time points.
p. Product use compliance assessment will occur at Check-in for at-home product acclimation and at each day during in-clinic confinement to ensure participants have met the minimum use requirements via and pharmacy log respectively.

Table 2: Pharmacokinetic Sampling, Physiological Heart Rate Assessments, and Subjective Effects Questionnaires on Days 1 through 6

Sampling Times (min) [a]	Blood for Nicotine PK	Blood for NNN PK	Heart Rate [b]	Subjective effects questionnaires [c]				
				Product Liking	Tobacco/Nicotine Withdrawal	Direct Effects of Product	Use the Product Again	mCEQ
-5	X	X	X		X			
3	X							
5	X	X	X	X	X	X		
7	X	X						
10	X	X						
15	X		X	X	X	X		
30	X		X	X	X	X		
45	X							
60	X		X	X	X	X	X	
120	X							
180	X		X	X				X

Abbreviations: mCEQ = modified Cigarette Evaluation Questionnaire; min = minutes; NNN = N-nitrosonornicotine; PK = pharmacokinetic; VAS = visual analogue scale.

a: Nominal sampling times for PK assessments of nicotine in plasma are relative to start of the morning *ad libitum* product use.
b: Heart rate measurements will be performed prior to the blood draw (approximately 1 minute prior to the scheduled blood draw time point) when scheduled at the same time.
c: Subjective effects questionnaires will be assessed on visual analogue scale (VAS) at nominal sampling times.

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse experience
AL	Abuse liability
ALCS	Altria Client Services LLC
$AUC_{(0\text{-}180)}$	Area under the nicotine concentration-time curve calculated using linear trapezoidal summation from time zero (defined as the start of product use) to 180 minutes (or the last quantifiable concentration during that interval)
$AUEC_{PL}$	Area under the effect curve for product liking from time zero (defined as the start of product use) to 180 minutes
BLQ	Below the lower limit of quantitation
C_0	Pre-product administration concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum measured plasma concentration over the duration of the measurement interval
CRA	Clinical Research Associate(s)
C_t	Corrected concentration
$C_{t\ uncorrected}$	Uncorrected concentration
CV	Coefficient of variation
DEP	Direct effects of product
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
E_{max}	Maximum response score to effect
$E_{max\text{-}DEP}$	Maximum Direct Effects of Product response in VAS score recorded during each product use
$E_{max\text{-}PL}$	Maximum product liking response in VAS score during during each product use
$E_{max\text{-}TNW}$	Maximum reduction response in VAS score from baseline pre-use and post-use (i.e., $VAS_{pre\text{-}use} - VAS_{post\text{-}use}$) for Tobacco/Nicotine Withdrawal questionnaire during each product use
EOS	End-of-study

Abbreviation	Definition
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPHC	Harmful and Potentially Harmful Constituent
HTS	Heated tobacco stick(s)
HTP	Heated tobacco product(s)
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional review board
Kel	Apparent first-order terminal elimination rate constant
LSM	Least squares means
mCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
mHCI	Modified Health Canada Intense
N/A	Not applicable
n	Number
NNN	N-nitrosonornicotine
NRT	Nicotine replacement therapy
OTC	Over-the-counter
PK	Pharmacokinetic(s)
PL	Product Liking
Q	Quartile
QA	Quality assurance
SAE	Serious adverse experience
SAP	Statistical Analysis Plan
SD	Standard deviation
SEM	Standard error of the mean

Abbreviation	Definition
SOP	Standard operating procedure
SRM	Study reference manual
t	Actual sampling time since product administration
t1	Actual sampling time since pre-product administration sampling
$T_{½}$	Terminal elimination half-life
T_{max}	Time of the maximum measured plasma concentration over the duration of the measurement interval
TNW	Tobacco nicotine withdrawal
UBCC	Usual brand combustible cigarette
VAS	Visual analogue scale
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

There is an overwhelming public health consensus regarding the "continuum of risk" among tobacco products – with cigarettes and other combustible products posing by far the highest risk, and non-combustible products posing substantially lower risk (Hatsukami et al., 2007). FDA, through its "Comprehensive Strategy" for regulating tobacco products (FDA 2017), and Altria, through its 10-Year Vision (Altria), are pursuing efforts to reduce individual and population harm by encouraging adults who would otherwise continue to smoke combustible tobacco products to switch to FDA authorized, non-combustible tobacco products that are considered to be lower on the continuum of risk.

Approximately half of the adult smokers in the United States are interested in less harmful alternatives to combustible cigarettes (Altria). To realize the optimum public health benefits of such products, it is important for them to be not only less harmful, but also acceptable to adult smokers. Nicotine pharmacokinetics is a component of adult smoker satisfaction and product acceptability (Jacobxon et al., 2021). Also, subjective effects evaluation such as product satisfaction, craving reduction, and psychological rewards inform on product use experience. Specifically, in FDA's final rule on Premarket Tobacco Product Applications and Record keeping Requirements, FDA indicated Product Liking as a key subjective endpoint for assessment of abuse liability of new tobacco products (A Rule by the Food and Drug Administration on 10/05/2021). FDA (Gottlieb, 2017), the former Institute of Medicine (Institute of Medicine, 2012), and public health researchers (Abrams et al., 2018), have also indicated that alternatives to combustible cigarettes should deliver nicotine in an amount and manner that is satisfying to adult smokers.

The test products used in this study are a type of HTP, which are also alternately referred to as Heat-Not-Burn Products. The non-combustible test product heats tobacco at lower temperatures without burning it, to produce an aerosol that delivers nicotine while significantly reducing the production of other Harmful and Potentially Harmful Constituents (HPHCs) (FDA 2019) compared to cigarette smoke.

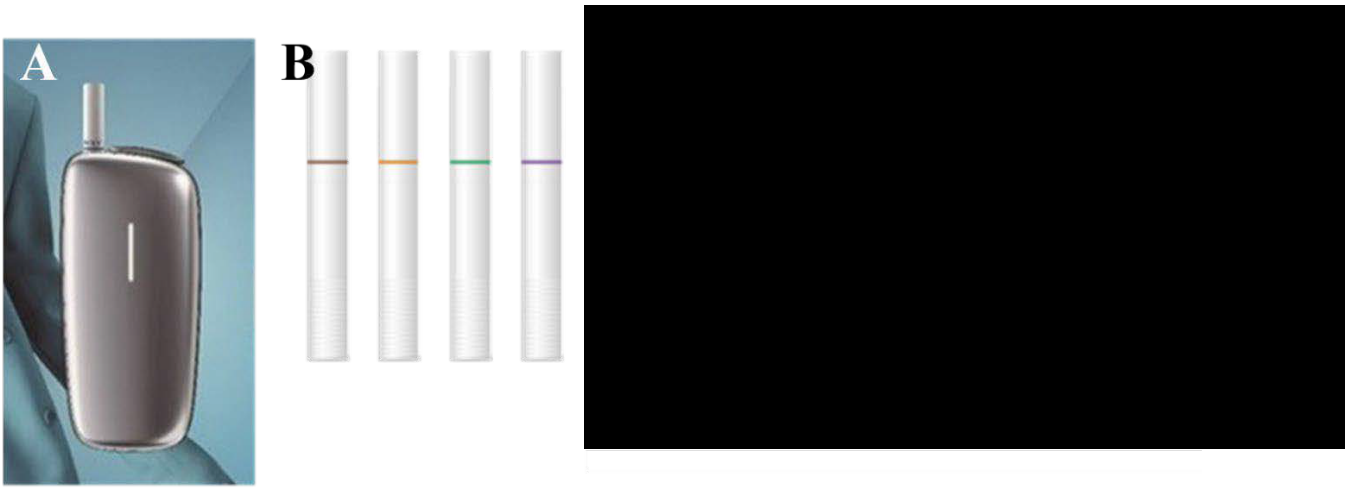
While there are no published data on current study product, two recent studies conducted by Yuki et al. (Yuki et al., 2018, Yuki et al., 2022) using earlier versions of Ploom brand of HTPs showed that BoE values were significantly reduced compared to combustible cigarette users in a 5-day confinement setting (n=60). Furthermore, the magnitude of the reductions in exposure to HPHCs observed in the HTP users (49–94%) were close to that observed for the smoking abstinence group (39–95%) (Yuki et al., 2018). In a second study, significant reductions in most BoE relative to the combustible cigarette users after switching to heated tobacco products for 5 days in confinement setting (n=80) were reported (Yuki et al., 2022). The magnitudes of reductions in exposure to most of the selected HPHCs observed in the HTP groups approached that observed in participants who abstained from smoking.

1.2 Study Product Background

1.2.1 Test Product

The test product is a prototype HTP intended for adult smokers as an alternative to combustible cigarettes. The HTP prototype consists of a durable hand-held battery-operated device and a disposable tobacco-containing stick that is inserted into the device (Figure 1). The stick consists of [redacted] Upon application of electrical power by the device, the tobacco in the stick undergoes controlled heating and a nicotine-containing aerosol is generated. This is a new type of inhalable tobacco product that provides a tobacco experience by heating tobacco without burning it.

Figure 1: Heated Tobacco Product



A: Device **B: HTS** **C: Cut-away view of assembled HTP**

Single-use tobacco-filled sticks (Figure 1) in either menthol or tobacco flavor varieties are inserted into the heating device (Figure 1). The stick, and therefore the tobacco, is heated and maintained at predetermined temperatures. As the stick is heated, an aerosol is produced, which is drawn through the stick and inhaled by the adult user. Each stick has a use duration of approximately 5 minutes, limited by the device. Once the predetermined use time is up, the stick is removed and disposed of. One device (Ploom® 3.1 prototype) and four HTPs, two tobacco flavored sticks and two menthol flavored sticks, containing different blends of tobacco will be tested in this study.

1.2.2 Reference Products

The study will use two reference products, which are participant's UBCC and Nicorette® Mint 4 mg nicotine gum, which will serve as high and low abuse liability reference products,

respectively. Nicotine PK and subjective effects of the Ploom® HTP will be compared with these reference products.

1.3 Summary of Findings to Date

Previous version and current Ploom HTP device and stick versions have been extensively evaluated over a period of approximately 24 months for collection of assessments (analytical aerosol data, clinical studies [PK and biomarkers], and in human expert panels assessing sensory experiences) in Japan and USA conducted by Altria. The functions of the device, such as temperature control, have been tested and verified. Both the device and sticks consistently performed as intended under test conditions, with no safety concerns raised.

1.3.1 Aerosol Chemistry

Analysis of the aerosol chemistry was performed in Japan among prototype HTS and a market leading cigarette in Japan; 51 constituents (HPHCs and metals) were assessed under controlled conditions (modified Health Canada Intense [mHCI] regimen, 55 mL puff volume, two seconds duration, taken every 30 seconds without vent blocking measures). More than half of the 51 constituents were not detected or not quantifiable. Where quantifiable, all aerosol constituents were lower (in most cases statistically lower) compared to market leading cigarette in Japan. Nicotine analysis in the aerosol of the prototype using the mHCI regimen indicated that the HTS deliver nicotine at a level comparable to or lower than other HTPs found in the global market and lower than the 1R6F reference cigarette.

1.3.2 Prototype HTP Temperature

The HTP prototype to be used in this study heats the tobacco in the stick to [redacted] These temperatures are lower than required for combustion to take place.

1.3.3 Clinical Studies

Ploom® HTP and HTS being used in this study are prototypes and they are not yet available commercially in the US. Therefore, all studies, described earlier, were conducted using a previous version of the Ploom® HTP outside the US.

1.4 Additional Information & Warnings

The packaging for electronically heated tobacco products (IQOS) recently marketed in the United States carried the following warning labels:

WARNING: This product contains nicotine. Nicotine is an addictive chemical
SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy.
SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.

SURGEON GENERAL'S WARNING: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, and Low Birth Weight.

The participants using their own brand of combustible cigarettes will be informed of the four US Surgeon General's Warnings required for cigarettes:

SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy.
SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
SURGEON GENERAL'S WARNING: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, and Low Birth Weight.
SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide.

A copy of the nicotine gum product insert, including instructions on single use, frequency of use and warning labels will be provided to participants by study staff for their review.

1.5 Study Rationale and Purpose

The purpose of this study is to characterize the plasma nicotine PK parameters, and subjective effects of four Ploom® HTPs (two menthol and two tobacco flavor HTS varieties) relative to participant's UBCC and nicotine gum (NRT) in adult menthol and non-menthol combustible cigarette smokers. The results of this study will allow assessment of nicotine PK and AL of the HTPs compared to UBCC and nicotine gum as a high and low AL reference products, respectively.

1.5.1 Study Design Rationale

This study will characterize plasma nicotine PK parameters and subjective assessments following HTP use with UBCC and nicotine gum as reference products (high and low abuse liability reference products, respectively) in healthy adult menthol and non-menthol combustible cigarette smokers.

Levels of experience with new products may influence product use and subsequent exposure. For that reason, individuals who do not currently use any HTP products will be enrolled. Each participant will be provided with an equal opportunity to become accustomed to the use of the HTPs during the product acclimation periods.

The subjective effects measures chosen for this study are standard measures to evaluate tobacco products. VAS measures of Product Liking, Tobacco/Nicotine Withdrawal, Direct Effects of Product, and Use the Product Again Questionnaire are included to capture the magnitude, onset, and offset of product effects during and after each use of the study products. The mCEQ is included as a measure of the overall effects of the test products.

2 OBJECTIVES

2.1 Main Objectives

- Characterize PK parameters of nicotine in plasma during and after a single *ad libitum* use of HTP (two menthol and two tobacco flavor varieties) relative to UBCC and the nicotine gum.
- Characterize Product Liking of HTP (two menthol and two tobacco flavor varieties) during and after a single *ad libitum* use relative to UBCC and the nicotine gum.
- Characterize additional subjective measures of HTP (two menthol and two tobacco flavor varieties) during and after a single *ad libitum* use relative to UBCC and the nicotine gum.
- Assess heart rate following the use of HTP (two menthol and two tobacco flavor varieties) relative to UBCC and the nicotine gum.
- Characterize product use of HTP during a single *ad libitum* use.
- Assess safety profiles of HTP (two menthol and two tobacco flavor varieties) compared to UBCC and nicotine gum with monitoring of adverse experiences, symptom-driven physical examinations, and relevant clinical laboratories as needed.

2.2 Exploratory Objectives

- Characterize NNN uptake and compare the difference during HTP and UBCC use.
- Assess additional Product Liking parameters during each morning *ad libitum* product use.

3 STUDY DESIGN

3.1 Study Design and Overview

This is a randomized, controlled, six-way crossover clinical study to characterize the nicotine PK and subjective effects of HTPs (2 menthol varieties, Products A and B; 2 tobacco flavor varieties, Products C and D) in adult menthol and non-menthol combustible cigarette smokers. The study will include participants' UBCC (Product F) and a nicotine gum (Product E) as high and low abuse liability reference products, respectively, to the HTP. Results of this study will help in determining abuse liability of HTP products in current smokers.

The study will include generally healthy adult males and females who smoke factory manufactured combustible cigarettes. This study will recruit approximately 60 participants (composed of approximately 30 menthol and 30 non-menthol adult smokers) in an attempt to obtain approximately 48 study completed participants (approximately 24 menthol and 24 non-menthol smokers). Every attempt will be made to enroll no less than 40% of either sex for menthol and non-menthol smokers, respectively. Enrolled participants will be randomized based on sex and their UBCC (menthol or non-menthol) to one of 6 product use sequences.

Adult participants will be between 22 and 65 years of age at screening, inclusive. Participants must have a history of smoking ≥ 10 to ≤ 30 menthol or non-menthol factory manufactured combustible cigarettes daily for at least 12 months prior to screening.

Screening

Screening will occur within 28 days prior to Day 1 and includes administering the FTCD, standard safety procedures, collection of baseline information, and a 5-day at-home HTP product trial period.

Enrollment Visit & At-home Product Trial

Enrollment visit (Day -6) will occur 5 days prior to Check-in (Day -1). Participants will receive the Ploom® HTP products for at-home product acclimation to become familiar with the product during the next 5 days. Training on how to use the Ploom® HTP device will be provided to each participant at the Enrollment visit. Participants will receive all four varieties of HTS on Day -6 and begin the at-home product trial. Participants are required to use each HTS variety at least once a day *ad libitum* for a minimum of 20 HTS uses over 5 days.

Check-in (Day -1) & Randomization

Participants will check-in on the morning of Day -1. Product use sequence randomization and assignment will also occur on Day -1. Participants will be randomized based on sex and their UBCC (menthol or non-menthol) to one of six product use sequences. Once participants are randomized to a product use sequence, product use sessions in confinement will start. Participants will remain in confinement at the clinic until completion of all study activities on Day 6.

Day -1 to Day 6

Starting on Day -1 (following Check-in) through Day 5, depending on the randomized product use sequence, participants will use their assigned product (HTP, UBCC, or nicotine gum) during an afternoon product use session. Participants will use the same assigned product to be tested during the next day's morning *ad libitum* product use PK test session (e.g., if a participant is assigned to Product A [HTP] as the product to be used in the morning *ad libitum* product use PK test session on Day 1, the participant will use Product A [HTP] during the afternoon product use session on Day -1). The afternoon product use session should be no more than approximately 6 hours long. Participants will be required to use the assigned study product at least once, but no more than six HTS, UBCC, or nicotine gum *ad libitum* per daily afternoon product use sessions. Participants will then be required to abstain from any tobacco- or nicotine-containing products for at least 12 hours prior to the start of the following morning's *ad libitum* product use PK test session.

Morning *ad libitum* product use PK test sessions will occur on the mornings of Days 1, 2, 3, 4, 5, and 6 (for a total of 6 morning *ad libitum* product use PK test sessions).

During the morning *ad libitum* product use PK test session, participants will use the assigned study product per their assigned product use sequence. Participants will use a single UBCC or HTP for 5 minutes *ad libitum* or use the nicotine gum for 30 minutes per product use instruction. Blood samples for PK will be collected prior to and for 3 hours following the start of each morning *ad libitum* product use PK test session. Heart rate measurements will be taken at specified time points during each morning *ad libitum* product use PK test session.

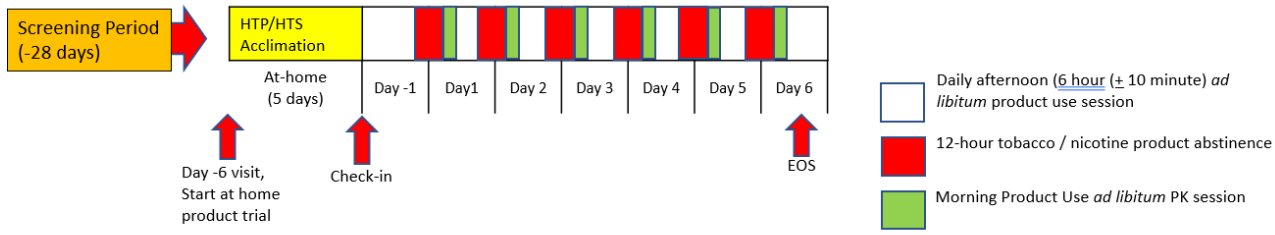
In addition, participants will complete subjective effects questionnaires (Product Liking, Tobacco/Nicotine Withdrawal, Direct Effects of Product, Use Product Again, and mCEQ) at designated time points during each morning *ad libitum* product use PK test session.

Participants will remain in confinement starting with Check-in on Day -1 until discharge after all study activities are completed on Day 6. Participants will not be forced to use the tobacco/nicotine products at any time during the study.

Study products and details are shown in Table 3.

The study schematic is presented in Figure 2.

Figure 2: Study Design Schematic



Day -6: Start at-home 5-day HTP/HTS product use acclimation
- Use each HTS at least one time each day for 5 days prior to check-in on Day -1.

Day -1: Check-in and product sequence assignment
- Participant is randomized to a product use sequence and begins afternoon product use of assigned study product *ad libitum* (up to 6 HTS, UBCC, & NRT gum) to be tested on the following day's morning product use *ad libitum* PK test session,

Days 1 – 6:
- Morning product use *ad libitum* PK test session (single product use 1 UBCC, 1 HTS, or 1 NRT gum) (UBCC and HTS use duration is 5 minutes and NRT gum is 30 minutes) (Total PK session -5 to 180 minutes)
- Daily afternoon product use sessions (6 hours (± 10 minutes)

Abbreviations: HTP: Heated tobacco product, HTS: Heated tobacco stick(s), NRT: Nicotine Replacement Therapy (nicotine gum), PK: pharmacokinetic, UBCC: Usual brand combustible cigarette.

3.1.1 Duration of Study

Study participation for each participant is expected to last up to 34 days, including a 28-day screening period (that includes a 5-day at-home HTP product trial period), and a 6-day in-clinic confinement period (from Check-in [Day -1] through the end-of-study [EOS] visit on Day 6).

3.1.2 Definition of Study Completion

End-of-study procedures will be performed as specified in the summary of events (refer to Table 1); participants who withdraw from the study early will have EOS/early termination (ET) procedures performed at the time of discontinuation. Participants with ongoing AEs will be followed until the AE is resolved or medically stable per Investigator's opinion; reasonable attempts will be made to follow up with participants. The participant's participation in the study will end once all study assessments and, if applicable, follow-up have been completed.

3.1.3 End of Study

The EOS is defined as the date when the last participant has completed all study procedures up to and including the EOS/ET as specified in the summary of events (Table 1).

3.2 Clinical Procedures

Participants will undergo screening procedures within 28 days prior to Day 1 to confirm that they meet study qualifications. Participants meeting all inclusion and none of the exclusion criteria will be selected for at home HTP acclimation and will have a product dispensing visit (Enrollment Visit) 5 days (Day -6) prior to Check-in at a time determined by the clinic. Participants will abstain from use of any nicotine- and tobacco-containing products from

Check-in until EOS except for the study products administered at scheduled times as defined in Table 1.

3.2.1 Questionnaire Training

At Check-in (Day -1), participants will complete one set of the subjective effects questionnaires (refer to the Appendices) in order to familiarize themselves with the questions, appropriate use of the VAS, and use of the computerized system. Participants will also be trained on a paper version of the questionnaires as a backup in case of computer issues during the study. Data from the training session will be recorded but not reported.

3.2.2 Product Use Training

Prior to sending participants home with the study HTP products on Day -6, participants must be instructed on the proper operation of the HTP device and how to insert/remove the HTS. Participants should receive instructions on how to use the NRT (gum) on Day -1 to ensure all participants know the proper use of the gum. Participants will not be provided any gum for the at-home product trial.

Training on how to use the Ploom® HTP device will be provided to each participant prior to the at-home HTP acclimation to ensure that all participants are familiar with how to use the device. The site staff will document the number of HTS dispensed for each participant. Product use will be recorded (i.e., number of HTS dispensed).

3.2.3 In-Confinement Afternoon Product Use Session

On the afternoon of Day -1 and on Days 1, 2, 3, 4 and 5 after the 180-minute test session, participants will participate in an approximately 6-hour *ad libitum* in-confinement afternoon product use session, using the product they are randomized to receive on the following morning during the morning *ad libitum* product use PK test session. During the afternoon product use session, each participant must use at least one but not more than 6 Ploom® HTS, pieces of nicotine gum, or UBCCs. Participants will abstain from all nicotine- and tobacco-containing products between each product use. Participants will use HTPs, combustible cigarettes and nicotine gum in separate rooms.

Note: Participants will abstain from all other nicotine- and tobacco-containing products except for the designated use of the study products, from Check-in to EOS (confined portion of the study).

3.2.4 Daily Product Use and Accountability of Used HTS

Daily HTP use will be tracked and recorded by the pharmacy or designated site staff and will be entered into the database. All used HTS will be collected and stored until the Clinical Research Associates (CRA) has had the opportunity to complete product reconciliation. Once the CRA has completed the reconciliation at the site the used HTS can be discarded per the sites' standard operating procedure (SOP). All Ploom® HTPs (devices) will be returned to the Sponsor at the end of the study. Unused HTS will be stored at room temperature until completion of the study

and destroyed per site SOP or returned to the Sponsor unless required by regulations to be held by the study site. Study Sponsor approval should be obtained prior to returning devices or study product as well as prior to destroying unused study product.

3.3 Test Session

3.3.1 Pharmacokinetic Assessments

On the morning of Days 1, 2, 3, 4, 5 and 6, depending on their assigned product use sequence, participants will use their assigned product (i.e., HTP, UBCC, or nicotine gum,) during the morning *ad libitum* product use PK test session. When assigned to use UBCC or HTP, PK assessment involves 5 minutes of *ad libitum* product use, during which time participants will smoke a single combustible cigarette without limitation on number of puffs and inter-puff intervals for up to 5 minutes or use one HTS without limitation on puffs or inter-puff intervals for up to 5 minutes (the devices automatically shut off five minutes from time of activation for Ploom® HTP). Study sites should ensure that the study participants only use their UBCC and any of the HTS for no more than 5 minutes. When assigned to use nicotine gum, participants will use this product for 30 minutes *ad libitum*, as per the manufacturer's use instructions (chew slowly until taste becomes strong, then rest between gum and cheek, start to chew again when the taste has faded. Keep chewing like this for the 30 minutes during the morning *ad libitum* product use PK test session). Serial venous blood samples will be collected at approximately -5, 3, 5, 7, 10, 15, 30, 45, 60, 120, and 180 minutes relative to the start of product use.

3.3.2 Physiological Heart Rate Assessments

Physiological heart rate assessments will be assessed at designated time points (see Table 2) during the morning *ad libitum* product use PK test sessions. Heart rate measurements will be performed prior to the blood draw (approximately 1 minute prior to the scheduled blood draw time point) when scheduled at the same time.

3.3.3 Subjective Measures

Subjective effects questionnaires (refer to the Appendices) will be administered during each morning *ad libitum* product use PK test session, concurrently with PK assessment on Days 1, 2, 3, 4, 5 and 6 to assess the effects of product use. Participants will have a questionnaire training session on Day -1 (refer to Section 3.2.1). On Days 1, 2, 3, 4, 5, and 6, participants will complete Product Liking, Tobacco/Nicotine Withdrawal, Direct Effects of Product, Use the Product Again, and mCEQ at various designated nominal time points for the blood draws (refer to Table 2).

3.4 Clinical Safety Evaluations

Clinical safety evaluations will be performed to ensure that participants meet the requirements of the study eligibility (Section 4) and to monitor participant safety. These evaluations will include physical examinations, vital sign evaluations, 12-lead ECGs, clinical laboratory assessments (clinical chemistry, hematology, urinalysis, and serology), urine drug and urine/breath alcohol

screens, and pregnancy test (all females) and follicle-stimulating hormone (FSH) tests (post-menopausal or symptomatic females only) at designated time points prior to and during the study. All reported AEs will be monitored and recorded throughout the study starting on Day -6 upon start of the At Home Product Trial (refer to Section 7).

Approximately 516.5 mL of whole blood will be collected from each participant during the course of the study. For all scheduled clinical laboratory tests, approximate blood volumes per sample are: 4 mL hematology and 8.5 mL chemistry (includes FSH, pregnancy, and/or serology when scheduled at the same time), for a total of approximately 12.5 mL for safety samples; 4 mL of blood for nicotine PK at each time point; and 10 mL of blood for NNN PK at each time point.

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all inclusion criteria to be eligible for study participation.

1. Participants must be informed of the nature and risks of the study and voluntarily give written informed consent prior to screening.
2. Healthy adult males and females ≥ 22 and ≤ 65 years of age, inclusive, at screening.
3. Participants must self-report currently smoking menthol or non-menthol factory manufactured combustible cigarettes. Participants will have a history of smoking ≥ 10 to ≤ 30 menthol or non-menthol factory manufactured combustible cigarettes daily for at least 12 months prior to screening. Prior to screening, brief periods (i.e., up to 7 consecutive days) of non-smoking within 90 days before Check-in (e.g., due to illness or participation in a clinical study where tobacco use was prohibited) will not be exclusionary at the discretion of the Investigator (other non-daily tobacco use, except for heated tobacco use, within 30 days prior to screening are not exclusionary).
4. Participants must be generally healthy, free of lifetime malignant tumors, and without clinically significant abnormalities as assessed by the Investigator based on the review of medical and surgical history, physical examination, vital signs, 12-lead ECG, and laboratory evaluations conducted at screening and Check-in, as applicable (refer to Table 1). A single repeat measurement/test may be performed to confirm vital signs, 12-lead ECG, and clinical laboratory tests abnormalities (i.e., to confirm that a participant is eligible).
5. Screening and Check-in systolic/diastolic blood pressure ≤ 150/90 mmHg measured after being seated quietly for at least 10 minutes. Two rechecks may be performed at the Investigator's discretion.
6. Urine cotinine ≥ 500 ng/mL at screening.
7. Exhaled carbon monoxide ≥ 10 ppm at screening.
8. Negative pregnancy test at screening and Check-in (Day -1) for all female participants.

9. Female participants who are sexually active and of childbearing potential (i.e., not surgically sterile at least 6 months prior to Check-in nor post-menopausal with amenorrhea for at least 1 year prior to Check-in and FSH levels consistent with post-menopausal status) must not be lactating and must have been using one of the following forms of contraception from 3 months before first study product administration through 30 days after the final administration of study product:

    - hormonal (e.g., oral, vaginal ring, transdermal patch, implant, injection) consistently for at least 3 months prior to Check-in, when used in combination with male condoms with spermicide (use of NuvaRing® is at the Investigator's discretion)
    - double barrier (e.g., condom with spermicide or diaphragm with spermicide) consistently for at least 2 weeks prior to Check-in
    - intrauterine device or system (utilize Investigator discretion regarding use of hormonal or nonhormonal devices) for at least 3 months prior to Check-in
    - exclusive partner who is clinically sterile (i.e., documented infertility or surgical sterilization; see below for additional information on sterility) or has been vasectomized for at least 6 months (inclusive) prior to Check-in

    Note: Sexual abstinence, defined as refraining from intercourse, is allowed when this is in line with the preferred and usual lifestyle of the participant. Female participants of childbearing potential who are not currently engaging in heterosexual intercourse must agree to use one of the above methods of birth control through completion of study, in the event that they have heterosexual intercourse during the course of the study.

10. Female participants who are of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to Check-in:

    - hysteroscopic sterilization with documentation of success with hysterosalpingogram
    - bilateral tubal ligation or bilateral salpingectomy
    - hysterectomy
    - bilateral oophorectomy
    - Essure®

    or be post-menopausal with amenorrhea for at least 1 year prior to Check-in and confirmed by FSH levels consistent with post-menopausal status.

11. Able to communicate effectively with the study personnel and willing to comply with the requirements of the study.

12. Willing and able to use all of the study products. This includes product use during the at-home product trial and the in-confinement product use sessions. If participants are

unwilling to use or unable to tolerate any of the study products they will not participate in this study.

4.2 Exclusion Criteria

Participants will be excluded from the study if there is evidence of any of the following criteria at screening or Check-in, or at any time during the study, as appropriate.

1. Use of any HTPs within the past 30 days prior to the screening visit; occasional use (i.e., not daily use) of other types of tobacco- or nicotine-containing products other than factory manufactured combustible cigarettes (e.g., roll-your-own cigarettes, e-cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) are allowed within the past 30 days prior to screening.
2. Any postponement of a quit attempt to participate in the study; or any attempts to quit smoking in the 3 months prior to Day -1 (Check-in).
3. Self-reported puffers (i.e., smokers who draw smoke from the combustible cigarette into the mouth and throat but do not inhale).
4. Poor dentition that prevents participant from using nicotine gum.
5. History or presence of any type of malignant tumor or clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, urologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other condition that, in the opinion of the Investigator, would interfere with the absorption, distribution, metabolism, or excretion of cotinine or jeopardize the safety of the participant or impact the validity of the study results.
6. Current evidence or any history of congestive heart failure.
7. Any other condition or prior therapy that, in the Investigator's opinion, would make the participant unsuitable for the study, or unable or unwilling to comply with the study procedures.
8. Clinically significant abnormal vital sign, physical examination (including oral cavity an oropharynx), medical history, or clinical laboratory finding(s), in the opinion of the Investigator.
9. Positive test for human immunodeficiency virus (HIV)-1 or HIV-2; or hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) consistent with current infection at screening.
10. Diabetes mellitus that is not controlled by diet/exercise alone, in the opinion of the Investigator. Fasting plasma glucose > 126 mg/dL (7 mmol/L) is exclusionary. One recheck may be performed for fasting plasma glucose values > 126 mg/dL but < 200 mg/dL.

11. An acute illness (e.g., upper respiratory infection, viral infection) requiring treatment with prescribed medicines within 2 weeks prior to Check-in.
12. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study through EOS.
13. History of alcohol abuse or drug abuse within 24 months prior to Check-in.
14. Consumption of alcohol-containing food or beverages within 48 hours prior to Check-in.
15. Positive screen for alcohol (breath or urine) or any of the following drugs of abuse (urine), regardless of the reason of use: amphetamines, methamphetamines, opiates, cannabinoids, or cocaine at screening or Check-in.
16. Fever (i.e., body temperature > 100.5°F) at screening or Check-in; 1 recheck may be performed at the Investigator's discretion.
17. Body mass index (NHLBI) > 40.0 kg/m^2 or < 18.0 kg/m^2 at screening.
18. Estimated glomerular filtration rate < 80 mL/minute using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Medscape) at screening.
19. Serum alanine aminotransferase ≥ 1.5 times the upper limit of normal and/or aspartate aminotransferase ≥ 2.0 times the upper limit of normal at screening; 1 recheck may be performed at the Investigator's discretion.
20. Female participants who are pregnant (positive pregnancy test at screening or Check-in), lactating, or intend to become pregnant from screening through EOS.
21. Use of prescription or over-the-counter (OTC) bronchodilator medication (e.g., inhaled or oral β-agonists) for treatment of any illness within 12 months prior to Check-in.
22. Use of antibiotics within 2 weeks prior to Check-in. Also refer to Section 5.7.1.
23. Use of medications known or are suspected to interact with cytochrome P450 2A6 (including, but not limited to, amiodarone, amlodipine, amobarbital, buprenorphine, clofibrate, clotrimazole, desipramine, disulfiram, entacapone, fenofibrate, isoniazid, ketoconazole, letrozole, methimazole, methoxsalen, metyrapone, miconazole, modafinil, orphenadrine, pentobarbital, phenobarbital, pilocarpine, primidone, propoxyphene, quinidine, rifampicin, rifampin, secobarbital, selegiline, sulconazole, tioconazole, tranylcypromine) within 14 days or 5 half-lives of the drug, whichever is longer, prior to Check-in.
24. Has taken other investigational drugs/products or participated in any clinical study for an investigational drug, device, biologic, or for a tobacco product within 30 days or 5 half-lives (if known) of the investigational product's PK, pharmacodynamic, or biological activity (if known), whichever is longer, prior to first administration of study product in

this study or is currently participating in another clinical study; or participation in > 2 ALCS-sponsored studies within the past 12 month period prior to Check-in.

25. Has received a vaccination within 14 days prior to Check-in.
26. Plasma donation within 7 days prior to Day 1.
27. Donation of ≥ 1 unit of blood or blood products (with the exception of plasma as noted), had significant blood loss > 450 mL, or received whole blood or a blood product transfusion within 56 days prior to Day -1.
28. Strenuous activity (as assessed by the Investigator) within 48 hours prior to Check-in.
29. Participant or a first-degree relative (i.e., parent, sibling, child, spouse) is a current or former employee of the tobacco industry or a named party or class representative in litigation with any tobacco company.
30. Participant or a first-degree relative (i.e., parent, sibling, child, spouse) is a current employee of the study site.
31. Unwilling or unlikely to comply with the requirements of the study.

4.3 Screen Failures

Participants who are discontinued from the study prior to study product administration will be considered screen failures.

If a qualified participant, including an alternate participant, leaves the study prior to first test product use (at home product trial), the participant may be enrolled into a subsequent cohort (at Investigator's discretion) if the enrollment is within 28 days of screening and the required at home product trial is completed prior to Check-in.

Screen failures will be recorded in the electronic data capture (EDC) system.

4.4 Participant Discontinuation

Participants will be advised that they are free to discontinue from the study at any time and/or withdraw consent. The Investigator may discontinue a participant if they feel this action is in the best interest of the participant. At the discretion of the Investigator, and in consultation with the Sponsor, a participant may be discontinued for failure to adhere to the requirements of the protocol.

If a participant discontinues early from the study and has used any study product provided by the Sponsor, all of the safety data normally required at the EOS should be obtained, unless the participant refuses or withdraws consent. Participants with AEs will be followed to a final outcome. Final outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (participant is lost to follow-up).

Participants discontinuing from the study will not be replaced. Participants enrolled in the Product Trial but failed at Check-in or dropped prior to randomization will not be replaced. Participants completing, discontinuing, or removed from this study cannot re-enter. Reasons for discontinuation may include:

- AE
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by participant
- Death
- Noncompliance with study product
- Other (reasons other than the above should be noted)

In the event of a participant's discontinuation, the Investigator will promptly notify the Sponsor and Medical Monitor and will make every effort to complete the EOS assessments. All discontinued participants with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow up with participants.

In addition, the Sponsor reserves the right to discontinue this study at any time. The Investigator, in collaboration with the Sponsor, reserves the right to discontinue the study for safety reasons at any time.

5 PARTICIPANT PRODUCT USE

5.1 Identity of Study Products

A description of the study products is presented in Table 3.

Table 3: Study Products

Study Product	Description	Route of Administration	Manufacturer	
			Device	Sticks
A	Ploom® 3.1 HTP - Menthol HTS; MX3 (681) (Test Product)	Inhalation	PT. Pegatron Technology	JTI
B	Ploom® 3.1 HTP - Menthol HTS; MX5 (706) (Test Product)	Inhalation	PT. Pegatron Technology	JTI
C	Ploom® 3.1 HTP - Tobacco HTS; R8 (120) (Test Product)	Inhalation	PT. Pegatron Technology	JTI
D	Ploom® 3.1 HTP - Tobacco HTS; RX4 (953) (Test Product)	Inhalation	PT. Pegatron Technology	JTI
E	Nicorette® 4 mg Mint Nicotine Gum (Reference Product)	Oral	N/A	N/A
F	Combustible Cigarette (menthol or non-menthol), participant's usual brand (Reference Product)	Inhalation	N/A	Various

The HTP (devices and sticks; Products A, B, C, and D) and nicotine gum (Product E) will be sourced by Altria Client Services LLC. HTS for Products A, B, C, and D were manufactured by Japan Tobacco International (JTI). Participants' UBCC (Product F) will be sourced by the participant prior to Check-in.

5.2 Products Administered

The HTPs consist of a portable device and disposable HTS that contains approximately 254 – 261 mg of material consisting of tobacco (cut-filler), water, flavors and humectants (propylene glycol and vegetable glycerin). The device is used to hold the stick and provide power to heat tobacco in the stick. Four HTS (i.e., four Ploom® device sticks) will be tested in the study along with nicotine gum and the participant's menthol or non-menthol UBCC will be used as the reference product for menthol and tobacco groups, respectively. Refer to Table 3 for test product and reference product information.

5.3 Method of Assigning Participants to Study Products

ALCS will generate the randomization schedule and the Medrio system will be utilized to randomize participants. Refer to Section 8.3 for a description of randomization methods. Eligible participants will be assigned to a product sequence according to the list of participant randomization assignments.

5.4 Measurements of Product Use Compliance

5.4.1 At-home Product Acclimation

Study participants will be provided with a Ploom® HTP device and the HTS's for at-home product acclimation. Product use compliance will be assessed and unused product (HTS) at Check-in by site staff and will be recorded.

5.4.2 Product Compliance in Confinement

The study products will be administered by delegated and trained site staff. All product uses will be under the supervision of the study site staff. Details regarding product administration, including the product administered and the date and time of administration, will be recorded.

5.5 Study Product Storage, Accountability, and Retention

5.5.1 Storage Conditions

All study products will be stored in a locked, limited-access area in the study site and kept at controlled room temperature (defined as 15° to 25°C [59° to 77°F], with excursions permitted to 30°C [86°F]). A sufficient supply of all products for each participant may be transferred and kept in a secure area in the clinic (e.g., locked drawer or cupboard) each day as necessary, with appropriate documentation of transfer noted as above.

5.5.2 Product Accountability and Retention

The Principal Investigator must ensure that all study product supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all study product shipped by Altria Client Services LLC or their representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all study product. Current dispensing records will also be maintained including the date and amount of study product dispensed and the participant receiving the study product. All remaining study products not required by regulations to be held by the study site will be destroyed per site SOP or returned to Altria Client Services LLC or their representative after the study is completed.

Participants will supply one unopened pack of their UBCC at Check-in to be used during the study. The storage and accountability of the cigarettes will be handled in the same way, as applicable, as the study product supplied by Altria Client Services LLC. In addition, site staff will verify participants' UBCC and document/label accordingly for each participant for use during the study. Site staff will make a color copy of the package of each participant's UBCC. Each participant will only be provided the UBCC supplied by that participant.

Site staff will coordinate shipping of the HTPs and nicotine gum from the Sponsor. Site staff will document the date each shipment was received and recorded in the inventory records. Site staff will document and reconcile the total number of products shipped to the site, the total number of study products used during the study, and the total number of unused study products remaining at

the end of clinical conduct. The site pharmacy where randomization is completed will retain and store 1 pack of each HTP type at the site until the final study report is completed.

All used HTS will be collected and stored until the CRA has had the opportunity to complete product reconciliation. Once the CRA has completed the reconciliation at the site the used HTS can be discarded per the sites SOP. All Ploom® HTPs (devices) will be returned to the Sponsor at the end of the study. Unused HTS will be stored at room temperature until completion of the study and destroyed per site SOP or returned to the Sponsor. Sponsor approval should be obtained prior to returning devices or study product as well as prior to destroying unused study product.

5.6 Packaging and Labeling

5.6.1 Study Product

All product preparation will be performed by the pharmacist or qualified and trained study staff.

5.6.2 Blinding of Product Assignment

Study participants will know when they are using their UBCC and the nicotine gum. However, participants will not be informed of which Ploom® HTS product they are using. Participants will not see the stick or device packaging.

5.7 Concomitant Medications and Procedures and Other Restrictions

5.7.1 Concomitant Medications and Procedures

Any concomitant medications taken from 30 days prior to Check-in (Day -1) through EOS/ET will be recorded.

Prohibited medications are included in the exclusion criteria (Section 4.2).

Stable doses (i.e., no dosage adjustments within 30 days prior to Check-in) of prescription or OTC medications required to treat an Investigator-approved disease or condition are permitted at the discretion of the Investigator. Hormonal contraceptives (e.g., oral, vaginal ring, transdermal patch, implant, injection) and hormonal replacement therapy are permitted. Occasional use of OTC analgesics (e.g., acetaminophen, ibuprofen), Milk of Magnesia®, antihistamines, and nasal decongestants are permitted as needed to treat AEs experienced by participants at the discretion of the Investigator. Note: acetaminophen dosage up to 650 mg/day will be permitted. Note that some decongestants might cause a positive drug screen result and therefore their use should be discouraged within five to seven days of those tests.

No concomitant procedures will be performed during the study unless approved by the Investigator. Medications taken for a procedure will also be included on the concomitant medication eCRF, as well as the procedure itself.

5.7.2 Other Restrictions

Participants will be instructed to adhere to the following restrictions:

- No tobacco- or nicotine-containing product use from Check-in until EOS except at the designated time when only the study products are allowed.
- No strenuous exercise is allowed for 48 hours prior to Check-in or during confinement. Participants will be instructed to refrain from strenuous physical activity that could cause muscle aches or injury, including contact sports.
- No food or beverages containing alcohol for 48 hours prior to screening or Check-in or during confinement.
- No food or beverages containing grapefruit for 14 days prior to Check-in or during confinement.
- No beverages or liquids of any kind (including water) are allowed during the morning *ad libitum* product use PK test session five-minute *ad libitum* product use or 30-minute nicotine gum use. An exception can be made if a participant starts coughing uncontrollably while smoking their combustible cigarettes or using the HTPs, in which case they will be allowed to drink water. Water will be provided as desired at all other times.
- On each of the study days, participants will be required to shower and will receive clean articles of clothing following the completion of study events that day.

5.7.3 Dietary Considerations

Starting on Day -1, meals and snacks will be served at appropriate times as determined by the clinic based on the time of Check-in.

Participants will be served a standard breakfast each morning and must complete breakfasts on the mornings of Days 1 - 6 at least one hour prior to the start of each test session. Participants are not allowed snacks during the 180-minute test session. Participants are not required to consume the entire breakfast. The breakfast menu should be consistent (same menu items) throughout confinement (Days 1 - 6). A standard lunch, dinner, and snack will be served at approximately the same time on each of Days -1-5.

6 STUDY ASSESSMENTS AND PROCEDURES

Participants will undergo study procedures and assessments at time points specified in the summary of events in Table 1 and Table 2. Additional information on procedures is presented in Section 3.2.

6.1 Medical and Surgical History

At screening, the Investigator or designee will collect each participant's complete medical and surgical history in the EDC system. Histories will be confirmed at Check-in to determine if any changes have occurred since screening. Tobacco use history (UBCC only) will be captured in the EDC system, but other tobacco use will be kept in the participants' source documents.

6.2 Demographic Characteristics

Demographic characteristics including sex, age, race, and ethnicity will be recorded at screening.

6.3 Physical Measurements

Height (cm) and body weight (kg) without shoes will be recorded. Body mass index will be calculated using the height and weight obtained at screening.

6.4 Pharmacokinetic Assessments

6.4.1 Plasma Nicotine Concentration Measurements

Plasma PK samples (total whole blood volume of approximately 504 mL from Days 1 through 6) will be collected at time points specified in the PK sampling schedule (Table 2). Blood sample collection, processing, and shipping details will be outlined in a separate Study Reference Manual (SRM).

The allowed window for PK blood sampling is indicated in Table 4.

Table 4: Window for PK Blood Sample Collection

Nominal Time	Allowed Window
< 0 minute	≤ ± 2 minutes
> 0 - 30 minutes	≤ ± 30 seconds
> 30 - < 45 minutes	≤ ± 1 minute
≥ 45 - < 120 minutes	≤ ± 2 minutes
≥ 120 - ≤ 180 minutes	≤ ± 5 minutes

Plasma nicotine concentrations will be analyzed by the validated procedure "The Determination of Nicotine, Cotinine, Trans-3'-Hydroxycotinine Concentrations in Human Plasma by LC-MS/MS" by [redacted] Sample analysis shall be conducted in compliance with the agreed upon protocol, analytical plan, and [redacted] Bioanalytical Laboratory's SOPs. The ICH

Harmonised Guideline M10, Bioanalytical Method Validation and Study Sample Analysis (24 May 2022) will be used as a reference for sample conduct.

6.5 Physiological Heart Rate Assessments

At the time points indicated in Table 2, seated heart rate will be measured (see Section 6.8.4 for additional details). When scheduled at the same time, heart rate measurements will be performed prior to the blood draw (approximately 1 minute prior to the scheduled blood draw time point).

6.6 Subjective Measures Questionnaires

At the time points indicated in Table 1 and Table 2, participants will complete the following questionnaires (using VAS, as applicable) on an electronic device:

- Product Liking Questionnaire (Appendix 1)
- Tobacco/Nicotine Withdrawal Questionnaire (Appendix 2)
- Direct Effects of Product Questionnaire (Appendix 3)
- Use the Product Again Questionnaire (Appendix 4)
- Modified Cigarette Evaluation Questionnaire (HTP, Cigarette, NRT/Gum) (Appendix 5)

All relevant software and staff training specific to the electronic questionnaires will be provided by the Sponsor. Data will be captured in the Medrio system, as supplied by the Sponsor or designee (Section 13.1). Paper data collection may also be used if necessary and data entry will be performed through Medrio. Details will be provided in the Data Management Plan. Any electronic device and any electronic data collection/recording used must meet all regulatory requirements, including 21 CFR Part 11.

6.7 Product Use

For UBCC use, the cigarette dispensed, the number of puffs per combustible cigarette, and the start time of the first puff and end time of the last puff will be documented for the 5-minute *ad libitum* product use during the morning *ad libitum* product use PK Test Session (manually documented). During the afternoon product use session (no more than approximately 6 hours afternoon *ad libitum* product use), the number of cigarettes used will be documented (manually).

For HTP use, the HTS dispensed, the number of puffs per stick, and the start time of the first puff and the stop time of the last puff, will be documented for the 5-minute *ad libitum* product use period during the morning *ad libitum* product use PK test session (manually documented). During the afternoon product use session (no more than approximately 6 hours *ad libitum* product use), the number of sticks used will be documented (manually).

For nicotine gum, the product dispensed, the start time of use (when participant places the gum in the mouth) and the use stop time (when participant takes the gum out of the mouth) will be documented for the 30-minute *ad libitum* product use during the morning *ad libitum* product use PK test session (manually documented). During the afternoon product use sessions (no more than approximately 6 hours *ad libitum* product use), the number of pieces of gum used will be documented (manually).

6.8 Safety Assessments

6.8.1 Adverse Experiences

Participants will be monitored for AEs according to Section 7.

6.8.2 Laboratory Tests

All clinical laboratory tests listed in Table 5 will be conducted by a laboratory accredited by Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments of 1988 [CLIA-88]) or at the clinic study site using CLIA-waived kits or procedures. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the administration of a first study product.

Participants will fast a minimum of 8 hours prior to clinical laboratory sample collection at screening.

At screening, if a participant has an out-of-range value for a clinical laboratory parameter that the Investigator believes is not clinically significant or the Investigator does not believe is correct (e.g., lab or specimen processing error), but the Investigator wants to confirm with a repeat laboratory test, a single repeat is allowed to confirm the initial result.

Additional safety laboratory tests may be conducted as needed by the Investigator to evaluate participant safety.

Table 5: Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Hematocrit	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Ketones
Red blood cell count	Alanine aminotransferase	pH
White blood cell count	Aspartate aminotransferase	Protein
Neutrophils (absolute and percent)	Total bilirubin	Blood
Lymphocytes (absolute and percent)	Total protein	Glucose
Monocytes (absolute and percent)	Blood urea nitrogen	Leukocyte esterase
Basophils (absolute and percent)	Creatinine	Nitrite
Eosinophils (absolute and percent)	Estimated glomerular filtration rate per the CKD-EPI (Medscape)	Bilirubin
Platelet count (estimate not acceptable)	Sodium	Urobilinogen
	Potassium	Microscopic analysis (performed if blood, leukocytes, nitrites, or protein are present)
	Carbon dioxide	
	Chloride	
	Glucose [a]	
	Uric acid	

a. Fasting for at least 8 hours

6.8.3 Other Tests

The following tests will be performed:

- Exhaled carbon monoxide
- Urine drugs of abuse (see Section 4.2 for minimum evaluation) and urine/breath alcohol screens
    - During the screening period, drugs of abuse and alcohol screens may not be repeated for eligibility
- Quantitative urine cotinine test
- Serology tests (i.e., HIV-1 and HIV-2 antibodies, HBsAg, and HCV with current infection
- Pregnancy test (all females): serum testing at screening and urine/serum testing at Check-in
- FSH (post-menopausal or symptomatic females only)

6.8.4 Vital Signs

Seated screening and Check-in vital sign assessments will include oral temperature (°C), respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg), and heart

rate (beats per minute). Blood pressure and heart rate will be measured after the participant has been resting quietly in a seated position for at least 10 minutes. Any clinically significant abnormal vital sign assessments requires at least 1 repeat measurement.

If assessed, a vital signs abnormality that is considered clinically significant initially and on confirmation, requires a participant to be discontinued from the study, requires a participant to receive treatment, or requires a change or discontinuation from the study product (if applicable) will be recorded as an AE.

6.8.5 Physical Examination

Comprehensive physical examinations (excluding genital, rectal, and breast examinations [unless indicated]) will be performed per Table 1; timing, and abnormal findings will be documented in the participant's eCRF. All comprehensive physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat (including oral cavity and oropharynx), respiratory system, cardiovascular system, gastrointestinal system, blood and lymphatic systems, and the musculoskeletal system.

Symptom-driven physical examinations will be performed per Table 1 timing and will focus on any AEs ongoing at the time of the examination.

An abnormal physical examination finding that is considered clinically significant and requires the participant to be discontinued from the study, requires the participant to receive treatment, or requires a change or discontinuation of the study product (if applicable) will be recorded as an AE.

6.8.6 Electrocardiograms

Participants must be resting quietly in a supine position or in the most recumbent position possible for at least 5 minutes before the screening 12-lead ECG is obtained.

The ECGs will be documented as normal, having a clinically insignificant abnormality, or having a clinically significant abnormality, by the Investigator or medically qualified designee.

Electrocardiogram assessment may include automated interpretation of the tracings (e.g., rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T-wave, and U-wave abnormalities). The Investigator or designee is responsible for reviewing and over-reading the ECG interpretation, for assessing whether the ECG machine interpretation findings are accurate, appropriate, normal or abnormal, and for providing corrected interpretations as appropriate. In addition, any abnormal ECGs will be assessed for clinical significance.

6.8.7 Tobacco Cessation Information

The Investigator or his/her designee, at screening and at the EOS/ET, will advise all participants that to reduce the health effects of tobacco, the best thing to do is to quit. The Investigator or his/her designee will refer all adult tobacco smokers to the Quit Assist® website (using information cards, participant handouts, etc.), which contains citations to a number of third-party information sources, including websites, telephone resources, and other organizations with additional information.

6.8.8 Appropriateness of Safety Assessments

Safety evaluations selected for this study are typical of those for this participant population and utilize widely accepted measures.

7 ADVERSE EXPERIENCES

An AE is defined as any untoward medical occurrence in a participant administered a study product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study product, whether or not thought to be related to the study product (E6[R2] 2018). This includes a newly developed, worsened preexisting, recurring intermittent or intercurrent illness, injury, or condition. For this study, a laboratory AE is defined as an abnormal laboratory finding that is determined by the Investigator to be clinically significant for that participant.

Events captured between screening and the first study product use (i.e., Product Trial) will be documented as baseline signs and symptoms (in medical history) and not AEs. All AEs occurring during this clinical study after the first use of the HTP during the Product Trial and through Day 6 or EOS/ET must be recorded in the eCRF, including the date and time of onset and outcome of each event. Events occurring between signing of the ICF and prior to the first use of study products during the product study will be documented as baseline signs and symptoms in the medical history.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgery permitted by the clinical study protocol and the condition(s) leading to this surgery are not AEs.

The subjective measures questionnaires are not designed for identifying or documenting AEs. Therefore, responses to any items in the subjective measures questionnaires will not be used for AE identification or evaluation.

No causal relationship with the study products or with the clinical study itself is implied by the use of the term “adverse experience.”

The procedures specified in Section 7.4 are to be followed for reporting SAEs.

7.1 Recording Adverse Experiences

Adverse experiences are to be recorded on the AE page of the eCRF. The following information will be recorded:

Assessment of whether or not the AE is an SAE (Section 7.2.1)

Assessment of AE severity (Section 7.2.2)

Assessment of AE relationship to study product (Section 7.2.3)

Action taken - categorized as study product use not changed, study product use reduced, study product interrupted, study product withdrawn, not applicable

Outcome - recorded as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown, as applicable

7.2 Assessment of Adverse Experiences

The Investigator will assess each AE for seriousness, severity, and relationship to study product.

7.2.1 Serious Adverse Experiences

The Investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE that results in any of the following outcomes (ICH 1995, 21CFR312.32):

- Death
- A life-threatening adverse study experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

“Life-threatening” means that the participant was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe.

“Persistent or significant disability/incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.

Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An example is allergic bronchospasm requiring intensive treatment in an emergency room or at home.

Note: SAEs require immediate reporting to the Sponsor and Medical Monitor. Refer to Section 7.4 for details.

7.2.2 Severity

The severity of an AE will be graded according to the following definitions (ICH 1995):

- Mild: The AE is easily tolerated and does not interfere with daily activity.
- Moderate: The AE interferes with daily activity, but the participant is still able to function.
- Severe: The AE is incapacitating and requires medical intervention. Note: This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning.

7.2.3 Relationship to Study Product

The relationship of an AE to the study product should be determined by the Investigator according to the following criteria (E6[R2] 2018, ICH 1995, Nebeker et al., 2004, Edwards and Aronson, 2000) (the strength of a causal association may be revised as more information becomes available):

Not related: Clearly and definitely due to extraneous cause (e.g., disease, environment).

Unlikely:

a Does not follow a probable temporal (i.e., time) sequence from use of study product.

b Does not follow a known pattern of response to the study product.

c Could plausibly have been produced by the participant's clinical state/underlying disease or other drugs or chemicals the participant received.

d Does not reappear or worsen when the study product is re-administered.

Possible:

a. Follows a reasonable temporal (i.e., time) sequence from use of study product.

b. Follows a known pattern of response to the study product.

c. Could also have been produced by the participant's clinical state/concurrent disease or other drugs or chemicals the participant received.

Likely:

a Follows a reasonable temporal (i.e., time) sequence from use of study product.

b Follows a known pattern of response to the study product.

c Could not readily have been produced by the participant's clinical state/concurrent disease or other drugs or chemicals.

d Follows a clinically reasonable response on withdrawal (de-challenge), i.e., disappears or decreases when the study product is stopped or reduced.

e Rechallenge information is not required to fulfill this definition.

Definitely:

a Follows a reasonable temporal (i.e., time) sequence from use of study product.

b Follows a known pattern of response to the study product.

c Cannot be explained by the participant's clinical state/concurrent disease or other drugs or chemicals.

d Follows a clinically reasonable response on withdrawal (de-challenge), i.e., disappears or decreases when the study product is stopped or reduced.

e Recurs with re-exposure to study product (rechallenge). NOTE: Re-exposure of the participant is NOT required, but the "certainly/definitely related" category may only be used when recurrence is observed.

7.3 Discontinuation due to Adverse Experiences

Any participant who experiences an AE may be discontinued at any time from the study at the discretion of the Investigator. Participants discontinued from the study due to an AE, whether serious or non-serious, should be followed by the Investigator until the clinical outcome of the AE is determined. The AE(s) should be noted on the appropriate eCRFs and the participant's progress should be followed until the AE is resolved or medically stable as determined by the Investigator. The Sponsor and Medical Monitor must be notified.

7.4 Reporting Serious Adverse Experiences

In the event of any SAE reported or observed during the study, whether or not attributable to the study product, site personnel will report it immediately (within 24 hours) by telephone and by fax or e-mail to the Sponsor and Medical Monitor in accordance with procedures described in the SRM and/or SAE study-specific procedure. Site personnel will follow up with a written report on the next working day. The Investigator must also inform the IRB, in compliance with GCP reporting guidelines, and the site monitor of an SAE, whether or not considered study related. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the study product. Information not available at the time of the initial report (e.g., end date, laboratory values) must be documented on a follow-up SAE form.

All SAEs should be followed to their resolution, with documentation provided to the Sponsor and Medical Monitor on a follow-up SAE Report Form.

7.5 Adverse Experiences /Serious Adverse Experience Follow-Up

Each AE, including clinically significant laboratory abnormalities, whether serious or non-serious, will be followed until resolved, determined that follow-up is no longer required (at the discretion of the Investigator) or the participant is lost to follow-up. Final outcome may be classified as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with

sequelae, recovering/resolving, or unknown, as applicable. Where appropriate, medical tests and examinations will be performed to document the outcome of the AE.

7.6 Pregnancy

Pregnancies will be captured if they occur in female participants from the time the participant is first exposed to the study product until EOS/ET.

A positive pregnancy test prior to enrollment will be documented as a screen failure. Pregnancy occurring in a female participant (after first HTP use during the Product Trial through Day 6 or EOS/ET) will be documented in a pregnancy form (provided separately by the Sponsor) and as a protocol deviation to the IRB.

Pregnancy itself is not an AE. The Investigator or designee will discontinue the pregnant participant from the study and will advise her to seek prenatal care and counseling from her primary care provider. The Investigator will refer her to the Quit Assist® website, which contains citations to a number of third-party information sources, including websites, telephone resources, and other organizations with additional information. Advice given will be documented in the participant's source document.

All pregnancies must be reported by telephone and by fax or email to the Sponsor and the Medical Monitor within 24 hours of the site's learning of the pregnancy or, at the latest, on the following workday.

The study site staff will request the pregnant participant notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the study site staff will follow up with the participant until the end of pregnancy, if in compliance with the site's SOPs and with the participant's consent. This request and the participant's response will be documented in the participant's source document. A final report of pregnancy outcome will be sent to the Medical Monitor and Sponsor.

8 STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the principles specified in ICH Topic E9 (CPMP/ICH/363/96).

Details of the statistical analysis will be provided in the Statistical Analysis Plan (SAP).

SAS software (Version 9.4 or higher, Cary, North Carolina) will be used for all data presentation and summarization including statistical analyses, summary tables, figures, and data listings. Statistical methods will be discussed in detail in the SAP.

8.1 Sample Size Calculation

The purpose of this study is to characterize the nicotine PK and subjective effects of four Ploom® HTPs in healthy adult menthol and non-menthol combustible cigarette smokers. Assuming an intra-subject variability of 60% for plasma nicotine C_{max} and AUC (Picavet et al., 2016) as well as a true geometric mean ratio of 100%, a sample size of 48 participants would result in a 90% CI of (83%, 121%). If true geometric mean ratio of 105% is assumed, a sample size of 48 participants would result in a 90% CI of (87%, 127%). Based on previously published literature, typical sample sizes range from 10 to 32 participants for studies examining the PK and subjective effects of tobacco/nicotine-containing product use (Carter et al., 2009, Cobb et al., 2010, Cox et al., 2001, Gray et al., 2008, Hardie et al., 2022, Hatsukami et al., 2004, Kotlyar et al., 2007, McDermott et al., 2023). Therefore, a sample size of approximately 48 participants (24 completed participants per each of the menthol and non-menthol groups) is considered adequate for the current study design.

8.2 Analysis Populations

Enrolled Population: All participants who signed the ICF. This population will include all screen failure participants.

Pharmacokinetic Population: All participants who used any study product and have baseline pre-use and at least one plasma nicotine concentration value after product use has started.

Subjective Measures Population: All participants who used any study product and have pre-use (Tobacco/Nicotine Withdrawal) and at least one post-use (Product Liking, Tobacco/Nicotine Withdrawal, Direct Effects of Product, Use the Product Again, and mCEQ) score.

Physiological Heart Rate Population: All participants who used any study product and have pre-use and at least one post-use physiological heart rate measurement during the morning *ad libitum* product use PK test session.

Product Use Population: All participants who used any study product and have at least one puff count value.

Safety Population: All participants who used any study product.

Additional details describing the analysis data sets will be provided in the SAP.

For any participant who is pregnant during the study, that participant's data will only be listed but will be excluded from all analyses.

8.3 Randomization

ALCS will prepare the randomization schedule. Participants will be randomized at 1:1:1:1:1:1 ratio into 1 of 6 sequences as listed below. At least 60 participants will be randomized to ensure approximately 48 completed participants, with approximately 24 menthol and 24 non-menthol cigarette smokers. Every attempt will be made to enroll no less than 40% of either sex for each cigarette flavor (menthol or non-menthol). Participants will be stratified by sex and cigarette type for each of the sequences.

A 6x6 Latin Square with the following sequences will be used for the randomization:

Sequence 1 = ABFCED

Sequence 2 = BCADFE

Sequence 3 = CDBEAF

Sequence 4 = DECFBA

Sequence 5 = EFDACB

Sequence 6 = FAEBDC

Participants will be randomized to the above sequences on the day of Check-in (Day -1).

8.4 Pharmacokinetic Analysis

8.4.1 Pharmacokinetic Parameters

Pharmacokinetic parameters for nicotine will be computed from the individual baseline-adjusted plasma concentrations applying non-compartmental methods using appropriate validated PK software (Phoenix WinNonlin Version 8.0.0.3176 or higher). Concentration values below the lower limit of quantitation will be set to one half of the limit of quantification.

The following PK parameters will be determined for each product following the morning PK *ad libitum* Product Use:

C_{max}:	Maximum measured plasma concentration over the duration of the measurement interval.
T_{max}:	Time of the maximum measured plasma concentration over the duration of the measurement interval. If the maximum value occurs at more than one time point within the time span specified, T_{max} is defined as the first time point with this value.

$AUC_{(0\text{-}180)}$:	Area under the nicotine concentration-time curve calculated using linear trapezoidal summation from time zero (defined as the start of product use) to 180 minutes (or the last quantifiable concentration during that interval).
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log linear period (e.g., three or more non-zero plasma concentrations).
$T_{½}$	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.

Baseline adjustment of plasma nicotine concentrations will be performed by using the following equation: $C_t = C_{t\ uncorrected} - [C_0 \times e^{-kel\ t1}]$, where:

C_t	Corrected concentration
$C_{t\ uncorrected}$	Uncorrected concentration
C_0	Pre-product administration concentration
Kel [£]	Apparent elimination rate constant obtained from each participant's uncorrected concentrations (for this estimation, values below the lower limit of quantitation [BLQ] are set to zero pre-administration and prior to the first measurable concentration and as missing thereafter)
t	Actual sampling time since product administration
t1	Actual sampling time since pre-product administration sampling

[£] Note: the adjustment is participant- and product-specific. If a Kel cannot be estimated for a participant, the mean Kel value from other participants for that product will be used.

After correction for pre-product administration values, some concentrations may be BLQ and some may be negative values. Negative values will be assigned a value of 0 in the analyses and all other values obtained will be reported as is even if these values are BLQ.

Maximum change from baseline for plasma NNN levels will also be reported following HTP and UBCC use.

8.4.2 Statistical Analysis

A linear mixed model for analysis of variance will be performed on the natural log-transformed PK parameters C_{max} and $AUC_{(0\text{-}180)}$ for nicotine to compare each HTP to the reference products, UBCC and nicotine gum (NRT), respectively. The model will include sequence, study product, and study day as fixed effects and participant-nested-within-sequence as a random effect. Sequence will be tested using participant-nested-within-sequence as the error term. Geometric LSM and 90% CIs will be provided for the PK parameters of C_{max} and $AUC_{(0\text{-}180)}$ by study product. Geometric LSM ratio, 90% CIs of geometric LSM ratio, and p-values will be provided for the study product comparisons among each of HTP products and the reference products (UBCC and gum [NRT], respectively) in C_{max} and $AUC_{(0\text{-}180)}$. The above statistical analyses will be performed using the appropriate SAS procedure. Descriptive statistics will be provided as appropriate.

Details of the statistical methods will be provided in the SAP.

8.5 Physiological Heart Rate Assessments

Descriptive statistics will be performed for physiological heart rate data collected during morning *ad libitum* product use PK test sessions.

8.6 Subjective Measures Analysis

8.6.1 Product Liking, Tobacco/Nicotine Withdrawal, and Direct Effects of Product Questionnaires

Responses to Product Liking, Tobacco/Nicotine Withdrawal and Direct Effects of Product questionnaires recorded as VAS scores, will be treated as continuous variables and summarized by study product and time point for each questionnaire item. For each questionnaire item, descriptive statistics including n, mean, standard deviation (SD), percent coefficient of variation (CV%), minimum, median, maximum, first quartile (Q1), and third quartile (Q3) will be reported. For Tobacco/Nicotine Withdrawal, the above-mentioned descriptive statistics for the difference from pre-use to post-use scores at each time point will also be reported.

The following subjective effects parameters will be determined:

$E_{max\text{-}PL}$	Maximum product liking response in VAS score during each morning *ad libitum* product use.
$E_{max\text{-}TNW}$	Maximum reduction response in VAS score from baseline pre-use to post-use (i.e., $VAS_{pre\text{-}use} - VAS_{post\text{-}use}$) for Tobacco/Nicotine Withdrawal questionnaire during each morning *ad libitum* product use.
$E_{max\text{-}DEP}$	Maximum Direct Effects of Product response in VAS score recorded during each morning *ad libitum* product use.

As an exploratory endpoint, the area under the effect curve from time zero (defined as the start of product use) to 180 minutes for Product Liking response ($AUEC_{PL}$) during each morning *ad libitum* product use will be determined.

For the maximum response score to Product Liking questionnaire ($E_{max\text{-}PL}$), the maximum reduction response to each question item in the Tobacco/Nicotine Withdrawal questionnaire ($E_{max\text{-}TNW}$), and the maximum response score to each question item in the Direct Effects of Product questionnaire ($E_{max\text{-}DEP}$) following each product use, a linear mixed model for analysis of variance will be performed. The model will include sequence, study product, and study day as fixed effects and participant-nested-within-sequence as a random effect. Sequence will be tested using participant-nested-within-sequence as the error term. The LSM, 90% CIs, and p-values will be provided for the study products in each response. For exploratory purposes, the LSM difference, 90% CIs for the difference, and p-values will be provided for the study product comparisons among each of HTP products and the reference products UBCC and gum (NRT), respectively.

8.6.2 Use the Product Again Questionnaire

Responses on the Use the Product Again questionnaire will be recorded as VAS scores and converted to categorical variables (-50 to < 0, 0, > 0 to 50). These categorical data will be summarized by study product using frequency count tables. The categorical score for the Use the Product Again questionnaire is calculated by subtracting 50 from the original VAS score (0 to 100). Both the original VAS scores and bipolar scores in each category will also be treated as continuous variables and summarized using descriptive statistics (n, mean, SD, CV%, standard error of the mean [SEM], minimum, median, maximum, Q1, Q3, and 90% CIs).

8.6.3 Modified Cigarette Evaluation Questionnaires (mCEQ)

The appropriate mCEQ (Appendix 5) will be administered on study days when the participant uses either HTP, nicotine gum, or UBCC. The mCEQ will be administered using a 7-point Likert-type scale and treated as a continuous variable. Responses on the mCEQ will be presented individually and as the following item domains (Cappelleri et al., 2007):

a Product use satisfaction: average of the response scores from items 1, 2, and 12;

b Psychological reward: average of the response scores from items 4 to 8;

c Aversion: average of the response scores from items 9 and 10;

d Enjoyment of the sensation: response score from item 3;

e Craving reduction: response score from item 11.

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, median, maximum, Q1, Q3, and 90% CIs) of the subscale factor scores will be provided by sex and by study product. Individual responses will be listed.

Details of the statistical analyses will be described in a separate SAP.

8.7 Product Use Analysis

Descriptive statistics will be provided for the product use:

- Afternoon product use sessions (no more than approximately 6 hours): number of HTS, UBCC, and nicotine gum used
- Start time of the first puff and stop time of last puff for each product use during a morning *ad libitum* product use PK test session.
- Puff count during the morning *ad libitum* product use PK test sessions for UBCC and HTP products

8.8 Safety Analysis

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) and summarized by study product for the number of participants reporting the product-emergent AE and the number of product-emergent AEs reported. An AE listing, including verbatim term, preferred term, study product, severity, and relationship to study product, will be provided.

The number of participants experiencing AEs and the number of AEs will be summarized by study product using frequency counts.

Safety data, including laboratory evaluations, and vital signs assessments will be summarized by time point of collection as appropriate and for available data.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data as appropriate.

Changes in physical examination findings and/or symptom-driven findings will be described in the text of the clinical study report.

Concomitant medications will be coded using the WHO Drug Dictionary.

For any participant who enrolled into the study and test positive for pregnancy, that participant's data will only be listed but will be excluded from all analyses.

9 ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IRB review, and regulatory review. The Investigator must inform the study participant that his/her study-related records may be reviewed by the above individuals without violating the participant's privacy of personal health information in compliance with Health Insurance Portability and Accountability Act of 1996 regulations.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to Clinical Investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical Investigator and IRB. By signing this protocol, the Investigator affirms to the Sponsor that the Investigator will maintain, in confidence, information furnished to him or her by the Sponsor and will divulge such information to the IRB under an appropriate understanding of confidentiality with such board.

10 QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor and [redacted] will implement and maintain quality control and quality assurance (QA) procedures with written SOPs to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

10.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with FDA CFR governing Protection of Human Participants (Title 21 CFR Part 50), IRBs (Title 21 CFR Part 56), and the ICH E6 Guidelines on GCP (CPMP/ICH/135/95) The study will be conducted under a protocol reviewed by an IRB; the study will be conducted by scientifically and medically qualified persons, and each participant will give his or her written, informed consent before any protocol driven tests or evaluations are performed.

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the participant or when the change(s) involve only logistical or administrative aspects of the study and are approved by the Sponsor.

10.1.1 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the participant, Investigator, or site staff.

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated “important,” requiring immediate notification to the Sponsor and Medical Monitor. The Investigator is responsible for ensuring that any known protocol deviations are recorded and handled as agreed.

All protocol deviations/violations that occur during the study will be evaluated prior to database lock for their severity and impact on participant safety and data integrity and will be taken into consideration when participants are assigned to analysis population.

10.2 Protocol Amendments

No deviations from this protocol will be permitted, except in a medical emergency. The Investigator and the Sponsor will discuss any amendment to this study. If agreement is reached concerning the need for modification, this agreement will be made in a formal amendment to the protocol.

All revisions and/or amendments to the protocol must be reviewed and approved, if applicable, in writing by the IRB.

All persons who are affected by the amendment to the protocol will be retrained.

10.3 Monitoring of Study

The responsible study monitor will contact and visit the Investigator as necessary, and they will be allowed, upon request, to inspect and verify all records of the study (e.g., source document, ICFs, eCRFs, regulatory documents) in a manner consistent with GCP and all other applicable state and federal law.

It will be the study monitor's responsibility to inspect the source documents to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRF. The monitor will verify that each participant has consented in writing prior to any study procedures being performed. Where the terms of the Informed Consent, GCP, and all other applicable state and federal law permit, the monitor should have access to laboratory test reports and other participant records needed to verify the entries on the eCRF. The Investigator (or designee) agrees to cooperate with the monitor to ensure that any issues detected in the course of these monitoring visits are resolved.

In addition, the Sponsor's oversight monitors, internal auditors (or designee), IRB reviewers, and government inspectors may evaluate the study and must be allowed access to eCRFs, source documents, and other study files.

The Investigator must notify the Sponsor (or designee) promptly of any inspections of the study or activities related to the study conducted by regulatory authorities, allow the Sponsor (or designee) to be present during the inspection, and promptly forward copies of inspection reports to the Sponsor (or designee).

11 ETHICS

11.1 Institutional Review Board/Independent Ethics Committee Approval

11.1.1 Ethics Review Prior to Study

This protocol and ICFs will be reviewed and approved in writing by the IRB prior to commencement of the study. The study will not be initiated without the approval from the IRB. As applicable, any amendments after protocol approval will be reviewed and approved by the IRB prior to implementation. The IRB operations are in compliance with Title 21 CFR Part 56. Notice that the IRB approved the protocol, ICF, and any applicable amendments to the protocol and ICF updates will be in the final study report.

11.1.2 Ethics Review of Other Documents

The IRB will approve all protocol amendments (except for Sponsor-approved logistical or administrative changes), written informed consent documents and document updates, participant recruitment procedures, written information to be provided to the participants, available safety information, information about payment and compensation available to participants, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB and regulatory authority as applicable.

11.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each participant. The participants must be given ample time and opportunity to inquire about details of the study, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each participant prior to any study procedures being performed. All prospective participants will also sign the verified clinical trial consent form and will be checked to verify they are not enrolled in another clinical study prior to the remaining screening procedures.

11.3 Confidentiality

All study sites and vendors will have signed confidentiality agreements with [redacted] will regard all information provided to the Investigator dealing with the study and information obtained during the course of the study as confidential.

[redacted] and the clinical site(s) will not supply to the Sponsor any participant names, initials, date of birth (except year), or other personal identifiers. All such information appearing on any study document must be redacted before a copy of the document is supplied to the Sponsor or [redacted] Study findings stored on a computer will be stored in accordance with local data protection laws. The participants will be informed during the consenting process that representatives of the Sponsor (or designee), IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws.

11.4 Ethical Conduct and Responsibility of the Investigator

The Investigator is responsible for ensuring that the clinical study is performed in accordance with GCP based on the current ICH Guideline for GCP, the corresponding sections of the US CFR governing Protection of Human Participants (Title 21 CFR Part 50), Institutional Review Boards (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and other applicable legal and regulatory requirements.

The Investigator should ensure that all persons assisting with the study are qualified for the duties assigned, adequately informed and trained on the protocol and amendments to the protocol, the study products, and their study related duties and functions.

The Investigator will maintain a list, including signatures, of sub-investigators and other appropriately qualified persons to whom significant study-related duties are delegated. Any personnel changes in this list during the course of the study will be documented. All study-related training will be documented.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Reporting and Case Report Forms

12.1.1 Case Report Forms

The Investigator will be provided with eCRFs, and will ensure all data from participant visits are promptly entered into the eCRFs in accordance with the specific instructions given. The eCRFs will be completed for each screened participant whether or not they have completed the study. The Investigator will assure complete and accurate entries on the forms. The Investigator must review and sign the eCRFs to verify the integrity of the data recorded.

12.1.2 Laboratory Data

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential all samples be analyzed at that laboratory. The Investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

12.1.3 Retention of Source Documents

Investigator-specific essential documents and all primary data and copies thereof (e.g., source documents, eCRFs, laboratory records, data sheets, correspondence, photographs, computer records, etc.), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the investigative site's archives for a minimum of 20 years after the completion or termination of the study. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. The study report and final database will be retained in [redacted] archives for a minimum of 20 years after the completion or termination of the study and will be available for inspection at any time by the Sponsor. At completion of the study (i.e., at issuance of final study report), the final data will be transferred to the Sponsor. Participant initials, serology results, date of birth (except year), and other personal identifiers will be redacted from this data transfer file; any such information removed will be documented at the time of transfer.

12.1.4 Study Report

A study report written consistent with ICH guidelines will be provided by [redacted] to the Sponsor. The report will include a description of the clinical conduct of the study, safety evaluation, analytical methods and results, and the statistical analysis described in the statistical methodology section of the protocol and the SAP.

At the time the draft study report is completed, [redacted] QA unit will audit the report against the SAS data and the raw data. At the completion of the audit, a QA report will be issued internally allowing any findings to be addressed before report finalization.

12.2 Retention of Essential Documents

The study essential documents must be maintained as specified in the ICH guidelines for GCP and the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two years have elapsed since the formal discontinuation of clinical development of the study product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

12.3 Termination of the Study

The Sponsor reserves the right to discontinue this study at any time. The Investigator, in collaboration with the Sponsor, reserves the right to discontinue the study for safety reasons at any time.

13 DATA MANAGEMENT

Data management activities will be detailed in the Data Management Plan and carried out by the [redacted] data management team according to its internally established SOPs. All data for this study will be captured in the Medrio system, as supplied by the Sponsor or designee. Medrio is a 21 CFR Part 11 compliant. Electronic CRF's will be developed according to the study protocol specifications and will follow ALCS Data Standards. Analytical data will be collected external to the database.

Data can be captured as either paper source or using the Medrio InClinic ePRO system for participant -complete data. Data captured on paper will be entered into the EDC system by the site. The participant completed InClinic ePRO data will be completed by the participant. All subjective measures questionnaire data will be captured directly via the Medrio InClinic ePRO system and will be treated as source data. All data captured will have an audit trail.

Programmed edit checks will be used to ensure the accuracy and integrity of the database. Edit checks will be programmed within the system to check for errors and discrepancies, such as missing data, data inconsistencies and inappropriate date ranges. Corrections will be made by the site as necessary prior to database lock. Database lock will occur after all reviews are completed, all queries resolved and there are no outstanding issues. Any changes to the data following database lock will be documented and approved by the Sponsor prior to unlocking the database to make the required changes.

The AEs will be coded using the most current version of MedDRA®. Concomitant medications will be coded using the most current version of the WHO Drug Dictionary. The versions will remain the same throughout the study. Coding will be reviewed by the Medical Monitor at [redacted] and ALCS.

All casebooks will be signed by the Investigator prior to database lock. Submissions casebooks will be extracted after database lock and provided to the site.

Upon completion of the study, the clinical data will be transferred to the Sponsor in SAS format with supporting SAS documentation according to the specifications of the Sponsor. Participant names, initials, date of birth (except year), and other personal identifiers will be removed from this data transfer file; any such information removed will be documented at the time of transfer.

13.1 Medrio ePRO

The subjective measures questionnaire data will be captured in the Medrio system, as supplied by the Sponsor or designee. Paper data collection may also be used if necessary and data entry will be performed through Medrio. Details will be provided in the Data Management Plan.

14 ADMINISTRATIVE INFORMATION

14.1 Financing and Insurance

Financing and insurance will be addressed in a separate agreement between the Sponsor and the Investigator.

14.2 Publication Policy

The Sponsor will retain ownership of all data. All proposed publications based on this study will be subject to Sponsor's approval requirements.

15 REFERENCES

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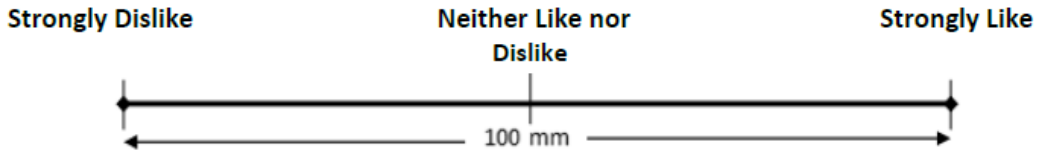
16 APPENDICES

Appendix 1: Product Liking Questionnaire

Product Liking Questionnaire

VAS Product Liking questionnaire is adopted from Drug Liking questionnaire.

Note: This question is paired with a VAS. The VAS is anchored with 'Strongly Dislike' on the left, 'Neither Like nor Dislike' in the center and 'Strongly Like' on the right. Participants place a vertical line at a place along the VAS based on how he/she feels in the moment.



Please respond to the question with how you feel right now in relation to the study product you are using today.

At this moment, how much do you like the product?

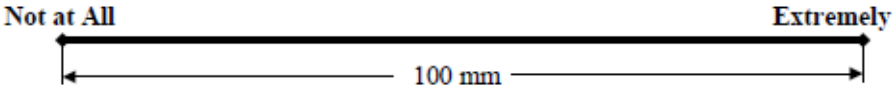
Product Liking Questionnaire Final v1.0
Effective Date: 14SEP2023

Appendix 2: Tobacco/Nicotine Withdrawal Questionnaire

Tobacco Nicotine Withdrawal Questionnaire

VAS Tobacco/Nicotine Withdrawal Scale (items on these scales have been adapted from Hughes & Hatsukami[1])

Note: Each question will be paired with a VAS. The VAS is anchored with "Not at All" on the left and "Extremely" on the right. Participants place a vertical line at a place along the VAS based on how he/she feels in the moment.



These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

1. Urges to smoke
2. Craving a Cigarette

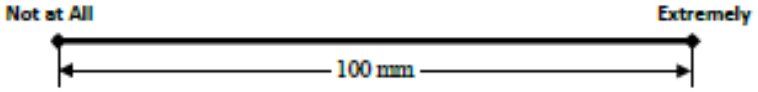
[1] Hughes JR, Hatsukami D (1986). Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry. 43(3):289-94.

Tobacco Nicotine Withdrawal Questionnaire v1.0
Effective Date: 01FEB2022

Appendix 3: Direct Effects of Product Questionnaire

Direct Effects of Product Questionnaire

VAS Direct Effects of Product Questionnaire (Items were selected based on measures of product effects used in previous trials with conventional cigarettes and other tobacco products.) Note: Each question will be paired with a VAS. The VAS is anchored with "Not at ALL" on the left and "Extremely" on the right. Participants place a vertical line at a place along the VAS based on how he/she feels in the moment.



1. Is the product "Pleasant" right now?
2. Is the product "Satisfying" right now?
3. Is the product making you feel "Calm" right now?
4. Is the product helping you "Concentrate" right now?
5. Is the product making you feel more "Awake" right now?
6. Is the product making you feel "Sick" right now?
7. Is the product reducing your "Hunger" for food right now?
8. Would you like "More" of the product right now?

Direct Effects of Product Questionnaire v1.0
Effective Date: 01FEB2022

Appendix 4: Use the Product Again Questionnaire

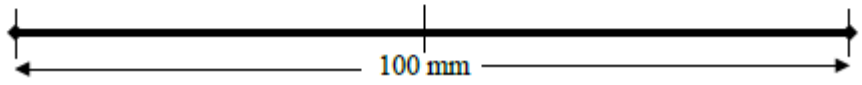
Use the Product Again Questionnaire

(Item adapted from abuse-deterrent formulation drug trials "I would want to take this drug again")

Please respond to the following statement based on your experience with the product you used today.

If given the opportunity, I would want to use this product again.

Definitely Would Not **Don't Care** **Definitely Would**



Use the Product Again Questionnaire v1.0
Effective Date: 01FEB2022

Appendix 5: Modified Cigarette Evaluation Questionnaires

Modified Cigarette Evaluation Questionnaire - HTP

Modified Cigarette Evaluation Questionnaire further modified for heated tobacco product (mCEQ-HTP)
*Thinking about the study product that you used today**,** please mark the number that best represents how using the heated tobacco product made you feel (1- not at all, 2- very little, 3-a little, 4-moderately, 5-a lot, 6-quite a lot, 7-extremely)*

1. Was using the heated tobacco product satisfying?
2. Did the heated tobacco product taste good?
3. Did you enjoy the sensations in your throat and chest?
4. Did using the heated tobacco product calm you down?
5. Did using the heated tobacco product make you feel more awake?
6. Did using the heated tobacco product make you feel less irritable?
7. Did using the heated tobacco product help you concentrate?
8. Did using the heated tobacco product reduce your hunger for food?
9. Did using the heated tobacco product make you dizzy?
10. Did using the heated tobacco product make you nauseous?
11. Did using the heated tobacco product immediately relieve your craving for a cigarette?
12. Did you enjoy using the heated tobacco product?

Modified Cigarette Evaluation Questionnaire for Heated Tobacco Product v1.0 01FEB2022

Modified Cigarette Evaluation Questionnaire (mCEQ) - Cigarette

Please mark the number that best represents how using the product made you feel (1 – not at all, 2 – very little, 3–a little, 4–moderately, 5-a lot, 6-quite a lot, 7-extremely)

Modified Cigarette Evaluation Questionnaire (mCEQ)

1. Was smoking satisfying?
2. Did the cigarette taste good?
3. Did you enjoy the sensation in your throat and chest?
4. Did smoking cigarettes calm you down?
5. Did smoking cigarettes make you feel more awake?
6. Did smoking cigarettes make you feel less irritable?
7. Did smoking cigarettes help you concentrate?
8. Did smoking cigarettes reduce your hunger for food?
9. Did smoking cigarettes make you dizzy?
10. Did smoking cigarettes make you nauseous?
11. Did smoking cigarettes immediately relieve your craving for a cigarette?
12. Did you enjoy smoking cigarettes?

Modified Cigarette Evaluation Questionnaire v1.0 01FEB2022

Modified Cigarette Evaluation Questionnaire-NRT

Modified Cigarette Evaluation Questionnaire further modified for oral TDN products
Please mark the number that best represents how using the product made you feel (1-not at all, 2-very little, 3-a little, 4-moderately, 5-a lot, 6-quite a lot, 7-extremely)

1. Was using the product satisfying?
2. Did the product taste good?
3. Did you enjoy the sensations in your mouth?
4. Did using the product calm you down?
5. Did using the product make you feel more awake?
6. Did using the product make you feel less irritable?
7. Did using the product help you concentrate?
8. Did using the product reduce your hunger for food?
9. Did using the product make you dizzy?
10. Did using the product make you nauseous?
11. Did using the product immediately relieve your craving for a cigarette?
12. Did you enjoy using the product?

Modified Cigarette Evaluation Questionnaire for OTDN v1.0 Effective Date: 01FEB2022

Appendix 6: Fagerström Test for Cigarette Dependence (FTCD)

Fagerström Test for Cigarette Dependence (FTCD)

For each question, enter the answer choice which best describes your response.

1. How soon after you wake up do you smoke your first cigarette
   - Within 5 minutes (3)
   - 6 – 30 minutes (2)
   - 31 – 60 minutes (1)
   - After 60 minutes (0)

2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema, etc.)?
   - No (0)
   - Yes (1)

3. Which cigarette would you most hate to give up?
   - The first one in the morning (1)
   - Any other (0)

4. How many cigarettes per day do you smoke?
   - 10 or less (0)
   - 11 to 20 (1)
   - 21 to 30 (2)
   - 31 or more (3)

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
   - No (0)
   - Yes (1)

6. Do you smoke if you are so ill that you are in bed most of the day?
   - No (0)
   - Yes (1)

Total Score: _____

Level of Nicotine Dependence:

- 0 – 2 = very low dependence
- 3 – 4 = low dependence
- 5 = moderate dependence
- 6 – 7 = high dependence
- 8 – 10 = very high dependence

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 86:1119-27.

Fagerstrom, Karl (2011): Determinants of Tobacco Use and Renaming the FTND to the Fagerstrom Test for Cigarette Dependence. Published by Oxford University Press on behalf of the Society for Research on Nicotine and Tobacco

Fagerstrom Test for Cigarette Dependence

ALCS Standard v1.0 Effective Date 19JUL2023

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Signing Complete	Security Checked	10/24/2023 6:58:48 AM
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