A Multi-site, Open-Label, Parallel-Group Study To Evaluate Changes In Tobacco-Related Biomarkers of Exposure and Biomarkers of Potential Harm with Use of Heated Tobacco Products Compared to Combustible Cigarettes in Adult Smokers

NCT06179290

05DEC2023

Clinical Study Protocol

A Multi-site, Open-Label, Parallel-Group Study To Evaluate Changes In Tobacco-Related Biomarkers of Exposure and Biomarkers of Potential Harm with Use of Heated Tobacco Products Compared to Combustible Cigarettes in Adult Smokers

Status: Amendment 4
Protocol Amendment 4 Date: 05-Dec-2023
Protocol Version: 5.0

Study Product: Ploom Heated Tobacco Product
Altria Client Services LLC Study Number: ALCS-REG-23-07-HT
CRO Study Number: CA41313

Sponsor:
Altria Client Services LLC
601 East Jackson Street
Richmond, Virginia 23219, USA

Sponsor Contact:
[redacted]

SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

Altria Client Services LLC Study Number: ALCS-REG-23-07-HT

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

DocuSigned by:
[redacted]
E180D66F308A4AFC933047E9DC5E47BD

12/7/2023

[redacted]
Altria Client Services LLC

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1295EF9A44684E998880248AAC8A98A3

12/6/2023

[redacted]
Altria Client Services LLC

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7864DEA49C72460B8BA47F38EA270A2E

12/6/2023

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Altria Client Services LLC

INVESTIGATOR AGREEMENT

Altria Client Services LLC Study Number: ALCS-REG-23-07-HT

A Multi-site, Open-Label, Parallel-Group Study To Evaluate Changes In Tobacco-Related Biomarkers of Exposure and Biomarkers of Potential Harm with Use of Heated Tobacco Products Compared to Combustible Cigarettes in Adult Smokers

By signing below, the Principal 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

_____	_____
Name, Qualifications Principal Investigator	Date

PROTOCOL AMENDMENT 4 REVISION HISTORY

1. The following table summarizes the updates made from Protocol Amendment 3, Version 4.0, 06-Nov-2023 to Protocol Amendment 4, Version 5.0, 05-Dec-2023

Schedule of Activities footnote "n"
Original
n. Blood collection for BoE and BoPH assessments; blood collection for COHb will occur on Days -1, 5, Days 30 (±3 days) and 60 (±3 days) and blood collection for CEVal will occur on Days -1 (baseline), 30 (±3 days) and 60 (±3 days). All blood collection for BoE and BoPH will occur at 21:30 (+/- 30 minutes). Blood collected on Day 1, Day 5, and on first day check-in for an overnight confinement for Day 60 (+/- 3 days) will be used for BoPH analysis.
Modified to
n. Blood collection for BoE and BoPH assessments; blood collection for COHb will occur on Days -1, 5, Days 30 (±3 days) and 60 (±3 days) and blood collection for CEVal will occur on Days -1 (baseline), 30 (±3 days) and 60 (±3 days). All blood collection for BoE and BoPH will occur at 21:30 (+/- 30 minutes). Blood collected on Day -1, Day 5, and on first day check-in for an overnight confinement for **Day 30 (+/- 3 days) and** Day 60 (+/- 3 days) will be used for BoPH analysis.
Rationale
Updated to clarify blood will be collected for BoPH analysis on Day 30 as well.
Schedule of Activities footnote "o"
Original
o. Product specific mCEQs for continue to smoke arms and HTP arms (mCEQ and mCEQ-HTP respectively) will be administered in the afternoon during confinement starting on Days -1, 3 and 5. During an ambulatory phase, a product specific mCEQ will be administered in the afternoon of the day subject checks in for overnight confinements for Day 30 (+/- 3 days) and Day 60 (+/- 3 days).
Modified to
o. An mCEQ for cigarettes for continue to smoke arms and HTP arms will be administered in the afternoon during confinement on Days -1. Starting on confinement Days 3 and 5, product specific mCEQ for continue to smoke arms and HTP arms (mCEQ and mCEQ-HTP respectively) will be administered in the afternoon. During an ambulatory phase, a product specific mCEQ will be administered in the afternoon of the day subject checks in for overnight confinements for Day 30 (+/- 3 days) and Day 60 (+/- 3 days).
Rationale
Updated as text to clarify which mCEQ will be administered and when.

Schedule of Activities footnote "g"
Original
g. Except for HTP Product Trial on Day -2, all subjects will continue to smoke their UBCC from the time of check-in on Day -2 until 23:00 and from 7:00 to 23:00 on Days -1.
Modified to
g. **Following the Product Trial session** on Day -2, all subjects will continue to smoke their UBCC from the time of check-in on Day -2 until 23:00 and from 7:00 to 23:00 on Days -1.
Rationale
Footnote was updated to reduce confusion around the day -2 activities.
Schedule of Activities footnote "v"
Original
N/A
Modified to
v. Subject disposition status will be documented at the end of confinement (Day 6) and at end of the study (Day 60)
Rationale
To capture subject disposition of subjects who have completed the confinement phase of the study.
Section 3.3.1 Screening
Original
Screening will be performed within 28 days of prior to check-in (Day -2). Medical and tobacco use histories, demographic data will be collected. Other screening procedures include a physical examination, vital signs, ECG, spirometry assessment, weight, height, and BMI, clinical laboratory assessments (hematology, serum chemistry, serology), routine urinalysis, urine/saliva drug screen, urine/breath alcohol screen, urine cotinine screen, and serum pregnancy testing and FSH assessment (for females as age and symptom appropriate). In addition, Principal Investigator will provide tobacco cessation information and QuitAssist® website at screening
Modified to
Screening will be performed within 28 days of prior to check-in (Day -2). Medical and tobacco use histories, demographic data will be collected. Other screening procedures include a physical examination, vital signs, ECG, spirometry assessment, weight, height,

and BMI, clinical laboratory assessments (hematology, serum chemistry, serology), routine urinalysis, urine/saliva drug screen, urine/breath alcohol screen, urine cotinine screen, and serum pregnancy testing and FSH assessment (for females as age and symptom appropriate). In addition, Principal Investigator will provide tobacco cessation information and QuitAssist® website at screening. **Subjects may be re-screened upon sponsor approval.**
Rationale
Rescreening criteria is added.
Section 3.3.4 Baseline Biological Sample Collection
Original
• Blood collected on Day -1, 5, and Day 60 (+/- 3 days) will be assessed for BoPHs (sICAM-1, WBC, and HDL-C)
Modified to
• Blood collected on Day -1, 5, **Day 30 (+/- 3 days)** and Day 60 (+/- 3 days) will be assessed for BoPHs (sICAM-1, WBC, and HDL-C)
Rationale
Text updated to add Day 30 to the second bullet point to ensure collection for BoPH analysis is clear.
Section 4.1 Inclusion Criteria
Original
2. Score 5 or higher (moderate dependence or higher) on the FTCD
Modified to
Deleted
Rationale
The study is designed for an adult smoking population with variable cigarette dependence, the inclusion criteria of FTCD scores for moderate to high cigarette dependence is not applicable to those subjects who have low cigarette dependence, but, may otherwise be eligible for this study. Thus, we removed the FTCD as an inclusion criterion but we will continue to collect FTCD scores at screening visits.
Section 8.1 Determination of Sample Size
Original

The sample size estimation is based on the data from a previous study (Haziza et al., 2020). Assuming a Type I error rate of 0.2% for each statistical test of a primary biomarker after multiplicity adjustment using the Bonferroni Method, a two-sided t-test for difference with unequal variances, the sample size of 60 per study arm will have 90% power to detect a statistically significant difference in the mean changes of creatinine adjusted values of the primary BoEs (Table 1) between the HTP arm in which adult smoker switched to HTPs for 5 days against the corresponding Continue Smoking arm.
Modified to
The sample size estimation is based on the data from a previous study (Haziza et al., 2020). Assuming a Type I error rate of 0.2% for each statistical test of a primary biomarker after multiplicity adjustment using the Bonferroni Method, a two-sided t-test for difference with unequal variances, **the sample size of 60 per HTP and Continue Smoking arms enrolled should ensure approximately 50 subjects complete Day 5 assessments and will have 90% power** to detect a statistically significant difference in the mean changes of creatinine adjusted values of the primary BoEs (Table 1) between the HTP arm in which adult smoker switched to HTPs for 5 days against the corresponding Continue Smoking arm.
Rationale
To provide clarity on determination of sample size for HTP and continue smoking arms

SYNOPSIS

Protocol Title	A Multi-site, Open-Label, Parallel-Group Study To Evaluate Changes In Tobacco-Related Biomarkers of Exposure and Biomarkers of Potential Harm with Use of Heated Tobacco Products Compared to Combustible Cigarettes in Adult Smokers
Brief Title	Changes in Biomarker of Exposure in Adults Who Smoke Cigarettes Switching from Cigarette Smoking to Ploom HTPs
Purpose	To evaluate changes in biomarkers of exposure (BoE) to harmful and potentially harmful constituents (HPHCs) in adult smokers who completely switch to Ploom HTPs compared to those who continue to smoke usual brand combustible cigarettes (UBCC).
Hypothesis	Completely switching from cigarette smoking to use of Ploom HTPs for 5 days will result in significant reductions in BoEs compared to continued cigarette smoking.
Objectives	The following objectives will be evaluated in each study group. Primary Objective: • To compare urinary and blood BoEs between the HTP arms and the corresponding Continue Smoking arm following 5 days of *ad libitum* use of HTPs or cigarettes in a confinement setting. Secondary Objectives: • To compare changes in urinary and blood BoEs between baseline and Day 5 (following 5 days of *ad libitum* use in a confinement setting) and Day 60 (±3 days; following 55 days of *ad libitum* use in an ambulatory setting) in the HTP arms and the corresponding Continue Smoking and Smoking Abstinence arms. • To compare changes in urinary and blood BoEs between the HTP arms and the corresponding Continue Smoking arm following 5 days of *ad libitum* use in a confinement setting and following 55 days of *ad libitum* use in an ambulatory setting. • To assess subjective effects in the HTP arms compared to the corresponding Continue Smoking arm following *ad libitum* use in confinement and ambulatory settings. • To compare changes in urinary and blood biomarkers of potential harm (BoPHs) between the HTP arms and the corresponding Continue Smoking and Smoking Abstinence arms following 5 days of *ad libitum* use in a confinement setting and following 55 days of *ad libitum* use in an ambulatory setting.

<table>
<tr><td></td><td>

To characterize use of HTPs during the 5-day confinement period and the 55-day ambulatory period.
To confirm the safety of Ploom HTPs during a 60-day use period.

Exploratory Objective:

To assess respiratory symptoms experienced while using the Ploom HTPs over 60 days.

</td></tr>
<tr><td>Endpoints</td><td>
Primary Endpoints:

Primary BoEs:

<table>
<tr><th>Biomarker</th><th>Matrix</th></tr>
<tr><td>Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)</td><td>Urine</td></tr>
<tr><td>Total N-nitrosonornicotine (NNN)</td><td>Urine</td></tr>
<tr><td>2-hydroxybutenylmercapturic acid (2-MHBMA)</td><td>Urine</td></tr>
<tr><td>3-hydroxypropylmercapturic acid (3-HPMA)</td><td>Urine</td></tr>
<tr><td>S-phenyl mercapturic acid (SPMA)</td><td>Urine</td></tr>
<tr><td>2-Hydroxyethyl mercapturic acid (HEMA)</td><td>Urine</td></tr>
<tr><td>1-aminonaphthalene (1-AN)</td><td>Urine</td></tr>
<tr><td>2-aminonaphthalene (2-AN)</td><td>Urine</td></tr>
<tr><td>2-cyanoethyl-mercapturic acid (CEMA)</td><td>Urine</td></tr>
<tr><td>3-hydroxybenzo[a]pyrene (3-OH-B[a]P)</td><td>Urine</td></tr>
<tr><td>3-hydroxy-1-methylpropylmercapturic acid (HMPMA)</td><td>Urine</td></tr>
<tr><td>4-Aminobiphenyl (4-ABP)</td><td>Urine</td></tr>
<tr><td>S-benzyl mercapturic acid (SBMA)</td><td>Urine</td></tr>
<tr><td>Carboxyhemoglobin (COHb)</td><td>Blood</td></tr>
</table>
Secondary Endpoints:

Secondary BoEs:

<table>
<tr><th>Biomarker</th><th>Matrix</th></tr>
<tr><td>Nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates) (NE)</td><td>Urine</td></tr>
<tr><td>N-(2-cyanoethyl) valine (CEVal)</td><td>Blood</td></tr>
</table>

Subjective assessments (modified cigarette evaluation questionnaire [mCEQ]) among subjects in both HTP and Continue Smoking arms during confinement and ambulatory phases.

</td></tr>
</table>

<table>
<tr><td></td><td>

BoPHs:

<table>
<tr><th>Biomarker</th><th>Matrix</th></tr>
<tr><td>Soluble intracellular adhesion molecule-1 (sICAM-1)</td><td>Blood</td></tr>
<tr><td>Total white blood cells (WBC)</td><td>Blood</td></tr>
<tr><td>High density lipoprotein cholesterol (HDL-C)</td><td>Blood</td></tr>
<tr><td>11-dehydrothromboxane B_2 (11-DTX-B2)</td><td>Urine</td></tr>
<tr><td>8-Epi-prostaglandin F2alpha (8-epi-PGF2a)</td><td>Urine</td></tr>
</table>

Daily product consumption from Day 1 to Day 5 (ie, number of cigarettes smoked per day and number of HTS used per day [HTSPD]).
Daily product consumption (self-reported) from Day 6 to Day 60 (±3 days) at Day 15 (±3 days), 30 (±3 days), 45 (±3 days), and 60 (±3 days) visits (ie, number of cigarettes smoked per day and average number of HTS used per day) via product accountability and study compliance assessment administered by site staff.
Safety assessments: Adverse experiences, symptom-driven physical examinations as needed, clinical laboratory as needed, and spirometry.

Exploratory Endpoints:

Respiratory Symptom Experience Scale assessments on Day -1, Day 30 (±3 days), and Day 60 (±3 days).

</td></tr>
<tr><td>Study Design</td><td>This is a multi-site, open-label, two-group (menthol and non-menthol), six-arm (HTP, Continue Smoking, and Smoking Abstinence arms within each group) randomized, clinical study to evaluate changes in BoEs in adult smokers who remain smoking, switch to the Ploom HTP, or abstain from smoking, for 60 days (5 days in clinic followed by a 55-day ambulatory phase).

Study Events and Procedures

Screening

Screening will be performed within 28 days prior to check-in (Day -2). Medical and tobacco use histories, and demographic data will be collected. Other screening procedures include a physical examination, vital signs, electrocardiogram (ECG), spirometry assessment, weight, height, and body mass index (BMI), clinical laboratory assessments (hematology, serum chemistry, serology), routine urinalysis, urine/saliva drug screen, urine/breath alcohol screen, urine cotinine screen, and serum pregnancy testing and follicle-stimulating hormone (FSH) assessment (for females as age and symptom appropriate). In addition, Principal Investigator will provide tobacco cessation information and QuitAssist® website at screening.</td></tr>
</table>

Product Trial

Day -2: Subjects will have an opportunity to try one Ploom HTS (menthol or tobacco HTS) based on the flavor categories of their UBCC before being randomized.

Baseline Measurements

Day -2 ~ Day -1: Following the Product Trial session, all subjects will smoke their UBCC until 23:00 on Day -2 and from 07:00 to 23:00 on Day -1. Baseline urine collection will start on the morning of Day -1 and will end on the morning of Day 1.

Randomization

Day -1: Subjects will be assigned to either a menthol or a non-menthol group based on their UBCC flavor category. Following group assignment, subjects will be randomized to one of the three arms based on gender and CPD stratification use (Low </= 16, or High > 16). The three arms are: Ploom HTP, continued cigarette smoking (Continue Smoking), and Smoking Abstinence arms in a 2:2:1 ratio.

Study Groups	Study Arms	Subjects (n)
Menthol	Ploom HTP Menthol HTS; MX3 (681)	60
	Continue Smoking	60
	Smoking Abstinence	30
Non-menthol	Ploom HTP Tobacco HTS; R8 (120)	60
	Continue Smoking	60
	Smoking Abstinence	30

Study Product Use

Day 1- Day 6 (confinement phase):

Subjects randomized to the HTP arms will use the assigned HTS exclusively (either menthol or tobacco flavor) starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days). At least 5 HTS will be used per day *ad libitum* between the hours of 07:00 through 23:00. Subjects may use product more than the minimum use requirement. Subjects will request one study product at a time from the pharmacy/designated site staff and return the used HTS prior to receiving another HTS.

Subjects randomized to the Continue Smoking arms will exclusively smoke their UBCCs *ad libitum* from 07:00 through 23:00 starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days). Subjects will request one cigarette at a time from the pharmacy/designated site staff and return the used butt prior to receiving another cigarette. There is no minimum required cigarette

	per day (CPD). Subjects randomized to the Smoking Abstinence arms will abstain from smoking or using any tobacco/nicotine-containing products for the entire duration of the study, starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days). Smoking and HTS use will be limited to a designated area of the site. Subjects in HTP arms will use an area separate from subjects in the Continue Smoking arms. Use of HTS or cigarettes will not be permitted from 23:00 to 07:00 each day starting from check-in (Day -2) until the end of confinement (Day 6). For product accountability and compliance, all smoked butts and all used HTS will be collected throughout the confinement phase (Day -2 through Day 5). All product uses, CPD, and HTSPD, will be documented. <u>Day 6 - Day 60 (±3 days) (ambulatory phase):</u> Subjects who have successfully completed the confinement phase of the study per protocol will continue to the ambulatory phase. Subjects in the HTP arms will be provided a Ploom HTP device and a 2-week supply of HTS based on their consumption during confinement (plus two additional packs of HTS) for use at home until the next scheduled visit. Subjects will exclusively use their assigned HTS *ad libitum* (at least 5 HTS per day; HTS arms), smoke their UBCC *ad libitum* (Continue Smoking arms), or continue to abstain from any tobacco/nicotine-containing products (Smoking Abstinence arms) starting from the morning of Day 6 (after discharged from the confinement phase). On Days 15 (±3 days) and 45 (±3 days), all subjects (from all 6 arms) will return to the site for study procedures. Subjects in the HTS arms will also receive a resupply of HTS. On Day 29 (±3 days) and Day 59 (±3 days), all subjects (from all 6 arms) will return to the site and start an overnight confinement for the 24-hour urine collection and other study procedures. Subjects in the HTP arms will receive a resupply of HTS on Day 30 (±3 days) prior to checkout. *Subjective Effects* • Subjects in continue to smoke and HTP arms will complete a product specific mCEQ (for cigarette and HTP) in the afternoon on Days -1, 3 and 5. • On Days 30 (±3 days), and 60 (±3 days), subjects in continue to smoke and HTP arms will complete product specific mCEQ in the afternoon when they check in for 24-hour urine collection.

	Exploratory Assessments • All subjects will complete the Respiratory Symptom Experience Scale on Days -1, 30 (±3 days), and 60 (±3 days) *Urine Collection* • Baseline 24-hour urine collection will start on the morning of Day -1 and completed on the morning of Day 1. • Subsequent 24-hour urine collection include: from the morning of Day 5 until the morning of Day 6. • Additional 24-hour urine will be collected at Day 30 (±3 days) and Day 60 (±3 days) during an ambulatory phase with an overnight confinement. • All urine voids will be collected over each 24-hour collection period (24-hour urine) for BoE analysis. During the confinement period Day -2 through Day 6, the 24-hour urine collection will begin at 07:00 (± 30 minutes) on Day -1 (baseline) and Day 5, and finishes the following morning at 07:00 (± 30 minutes) on Day 1 and Day 6. During overnight confinement in the ambulatory period Day 30 (±3 days) and Day 60 (±3 days), the 24-hour urine collection will begin following check-in (± 30 minutes). For further 24-hour urine collection procedures please refer to the Sample Handling Manual. *Urine Creatinine* • Urine creatinine will be measured in each 24-hour urine collection and used to adjust the concentration values of urine BoEs. *Blood Sample Collection* • A blood sample will be collected on Days -1 and 5 at approximately 21:30 (+/- 30 minutes). The sample will be used for COHb analysis and the remaining sample will be banked for exploratory endpoint analysis. Baseline blood sample collected on Day -1 will also be assessed for CEVal. • Blood samples will be collected on Days 30 (±3 days), and 60 (±3 days) for COHb and CEVal analysis. Blood drawn on Days 30 (±3 days) and 60 (±3 days) will also be used to assess CEVal as a marker for study compliance. *Product Use and Compliance* For subjects in the HTP and Continue Smoking arms, product use will be documented on Days 15 (±3 days), 30 (±3 days), 45 (±3 days), and 60 (±3 days). For all subjects, study compliance assessment will be performed by the site staff on product usage and compliance during these return visits. Compliance measures for all subjects will include blood

<table>
<tr><td></td><td>N-(2-cyanoethyl) valine (CEVal), exhaled CO (eCO), and urinary CEMA.

Any illicit use of any non-study related tobacco- or nicotine-containing products or sharing of study products will be strictly prohibited and may be grounds for immediate termination from the study.</td></tr>
<tr><td>Study Population and Sample Size</td><td>• This study will enroll healthy adult (22- 65 years of age) male and female (every attempt will be made to enroll no more than 60% of either gender in each arm) self-affirmed either menthol or tobacco variety combustible cigarette smokers with an average daily consumption of at least 10 but no more than 30 factory manufactured combustible cigarettes for at least 12 months prior to Screening.

• The study will enroll 150 subjects per group (menthol and non-menthol) for a total of 300 subjects. Within each group, subjects will be randomized to one of three arms: HTP arm (n=60 each), Continue Smoking arm (n=60 each), and Smoking Abstinence arm (n=30 each) following a 2:2:1 ratio to obtain at least 50 completers in each of the HTP and Continue Smoking arms for the confinement phase.</td></tr>
<tr><td>Study Products and Route of Administration</td><td>Subjects will be randomized to one of the following arms:

<table>
<tr><th>Study Groups</th><th>Study Products/Arms</th><th>Route of administration</th><th>Test or Reference</th></tr>
<tr><td rowspan="3">Menthol</td><td>Ploom 3.1 HTP Menthol HTS;</td><td>INH</td><td>Test</td></tr>
<tr><td>MX3 (681) Menthol UBCC</td><td>INH</td><td>Reference</td></tr>
<tr><td>Smoking Abstinence</td><td>NA</td><td>NA</td></tr>
<tr><td rowspan="3">Non-menthol</td><td>Ploom 3.1 HTP Tobacco HTS; R8 (120)</td><td>INH</td><td>Test</td></tr>
<tr><td>Non-menthol UBCC</td><td>INH</td><td>Reference</td></tr>
<tr><td>Smoking Abstinence</td><td>NA</td><td>NA</td></tr>
</table>
Abbreviation: HTP = Heated tobacco product, HTS = Heated tobacco stick, INH = Inhalation, NA = Not Applicable, UBCC = Usual brand combustible cigarette.</td></tr>
<tr><td>Statistical Methods</td><td><u>Statistical Analysis and Data Summarization</u>

In each group, all data will be listed by subject, arm, and study day, and summarized by arm and study day. 24-hour urinary BoE, blood COHb, and blood CEVaL biomarker data will be listed and summarized. Absolute and percent change from baseline values will be</td></tr>
</table>

	listed and summarized as appropriate. Descriptive statistics (number of observations [n], n missing, arithmetic mean [mean], median, standard deviation [SD], standard error of mean [SEM], minimum, maximum, Q1, Q3, coefficient of variation [CV]% and 95% confidence interval [CI]) will be used for continuous data variables and frequency counts (n and percentage) for categorical data variables as described in the statistical analysis plan (SAP). Geometric means will also be provided for original biomarker values. Figures will be used to display the data graphically. Demographics, smoking history, baseline daily cigarette use, mCEQ, spirometry results, Respiratory Symptom Experience Scale, and baseline Fagerström Test for Cigarette Dependence (FTCD) scores will be summarized overall and by group, with descriptive statistics for continuous variables and frequency counts and percentage for categorical variables will be provided. **Biomarkers of Exposure** In each group, linear mixed models for analysis of covariance (ANCOVA) will be used to compare the Day 5, Day 30 (±3 days), and Day 60 (±3 days) BoE values between arms as described in the study objectives ie, each HTP arm compared to the corresponding Continue Smoking arm, or compared to the Smoking Abstinence arm. In the statistical models, the change from baseline value of a BoE will be included as a dependent variable; arm and gender will be included as fixed effects; and baseline values of corresponding BoE will be included as covariates. The least-squares means (LSM) difference, 95% CI for the LSM difference between the Test and Reference, and p-values will be provided. **Product Use** The number of HTS used per day and the number of cigarettes smoked per day during the confinement phase, and the average number of HTS per day and the average number of cigarettes smoked per day during the ambulatory phase will be listed and summarized by study product using descriptive statistics, as appropriate. **Safety Data** Clinical safety evaluations will be performed to ensure that the subjects meet the requirements of the study and to monitor subject safety. Screening safety evaluations will include a physical examination, a 12-lead ECG, spirometry, a clinical laboratory assessment (serum chemistry, hematology, and urinalysis), serology, vital signs measurements, a urine/saliva drug screen, a urine/breath alcohol test, a serum pregnancy test (females only), and FSH (postmenopausal females only) tests. On-study safety evaluations will include vital signs measurements, urine/saliva drug screens, urine/breath alcohol tests, and urine/serum

	pregnancy tests (females only). End of Study (or early termination) safety evaluations will include spirometry and vital signs measurements. Adverse experiences (AEs) spontaneously reported by the subjects in all groups or observed by the site staff will be monitored from the time of the first test product use during the Product Trial session on Day -2 until the End of Study (or early termination). AEs reported from the time of signing the ICF and prior to first study product use on Day -2 will be recorded as Medical History. Any concomitant medications taken from 30 days prior to Screening through the End of-Study (or early termination) will also be recorded. AE data will be coded (to the lowest level term) with the Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be listed by subject in data listings. Frequency counts of AEs will be provided by body system, preferred term, and study product. Frequency counts of AEs will also be summarized by severity and relationship to study product.

SCHEDULE OF ACTIVITIES

Study Procedure	Screening	Study Period (Confinement Phase)							
	Days -30 to -3	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Inclusion/exclusion criteria	X	X							
Verified clinical study consent	X								
Informed consent	X								
Demographics	X								
Medical, surgical, tobacco/nicotine use history	X [a]	X [b]							
Concomitant medication	X	X	X	X	X	X	X	X	X
FTCD	X								
Height, body weight, and BMI [c]	X								
Physical examination [d]	X								
Adverse experience assessment		X	X	X	X	X	X	X	
Vital signs (BP, HR, RR, oral temperature)	X	X							X
12-lead ECG	X								
Clinical laboratories (hem, chem, UA)	X								
Serology (HIV and hepatitis screen)	X								
Serum/urine pregnancy test (all females)	X [e]	X							X
FSH [f] (postmenopausal or symptomatic females only)	X								
Spirometry assessment	X								
Tobacco cessation information [s]	X								
eCO[u]	X								
Respiratory Symptom Experience Scale			X						
Blood collection			X [n]					X [n]	
Urine/saliva drugs and urine/breath alcohol screen	X	X							
Urine cotinine screen	X								
Randomization (based on gender and CPD stratification)			X						
Usual brand cigarette use		X [g, h]	X [g, h]	X [i]	X [i]	X [i]	X [i]	X [i]	X [i]
HTP product trial (for all subjects)		X							
HTP use per protocol (HTP arms) [j]				X	X	X	X	X	X
mCEQ			X			X		X	
24-hour urine collection [k]			X	X				X	X
End of confinement [v]									X
Transition to ambulatory phase									X [l]

Study Procedure	Study Period (Ambulatory Phase)			
	Day 15 (± 3 days)	Day 30 (± 3 days)	Day 45 (± 3 days)	Day 60 (± 3 days)
HTP resupply	X	X	X	
Concomitant medication	X	X	X	X
Adverse experience assessment	X	X	X	X
eCO[u]	X	X	X	X
Spirometry assessment				X
Respiratory Symptom Experience Scale		X		X
mCEQ[o]		X		X
Blood collection		X [m, n]		X [m, n]
Urine/serum pregnancy test (for all females)	X	X	X	X
Usual brand cigarette use (Continue Smoking arms only)		X		
HTP use per protocol (HTP arms only)		X		
Product accountability [p]	X	X	X	X
Study compliance assessment [q]	X	X	X	X
Overnight confinement and 24-hour urine collection [r]		X		X
Tobacco cessation information [s]				X
End of study and early termination assessments [t,v]				X

Abbreviations: BMI = body mass index; BoE = biomarker of exposure; BoPH = biomarker of potential harm, BP = blood pressure; CEVal = N-(2-cyanoethyl) valine; chem = serum chemistry; CPD = cigarettes per day; ECG = electrocardiogram; eCO = exhaled carbon monoxide; EOS= end of the study; ET= early termination; FSH = follicle-stimulating hormone; FTCD = Fagerström Test for Cigarette Dependence; hem = hematology; HIV = human immunodeficiency virus; HR = heart rate; HTP = heated tobacco product; HTS = heated tobacco stick(s); mCEQ = modified cigarette evaluation questionnaire; UBCC = usual brand combustible cigarette, RR = respiratory rate; UA = urinalysis.

a. The following characteristics of the subject's usual brand will be documented: brand, brand style, and flavor. The number of uses per day (single number, not a range) will also be documented. Subjects will bring with them a new pack of their most commonly used cigarettes. The pack will be color photocopied and the copy will be placed in the source documents at Screening.
b. Interim medical history.
c. BMI will be calculated using subject's weight and height.

d. Physical examination is required at screening. Between Day -2 and End of Study/Early Termination a symptom driven physical exam may be completed if new symptom(s) occur during the study that were not present during the screening physical examination or to investigation an adverse experience at the Principal Investigator's discretion.

e. Serum pregnancy test for all females at Screening. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

f. To confirm postmenopausal status in self-reported postmenopausal females only.

g. Following the Product Trial session on Day -2, all subjects will continue to smoke their UBCC from the time of check-in on Day -2 until 23:00 and from 7:00 to 23:00 on Days -1.

h. Product use (UBCC and HTP) will not be permitted from 23:00 to 07:00 each day during the study from check in (Day -2) until Day 5.

i. Subjects in the Continue Smoking arms will be allowed to smoke UBCC upon request to the clinic staff but will only be allowed 1 cigarette at a time and will be instructed to return each cigarette butt upon completion

j. During confinement, subjects in HTP arms will request both HTP device and HTS from the pharmacy and use the assigned HTSs at least 5 times a day and will be instructed to return each used HTP device and HTS upon completion; additional HTP use is permitted after subject meets the minimum use criteria.

k. Two 24-hour urine collections will occur starting on the Day -1 and end on the morning of Day 1 (baseline) and again on the morning of Day 5 and end on the morning of Day 6; collection will start after the first morning void and any void prior to 07:00 (+/- 30 minutes) and finishes the following morning with the last void collected at approximately 07:00 (+/- 30 minutes) (including first morning void).

l. Subjects who have completed all study procedures per protocol will transition to ambulatory phase of the study following completion of 24- hour urine collection on Day 6; subjects in HTP arms will be discharged to home with HTP device and sufficient amount of HTS to last until next schedule visit on Day 15 (±3 days).

m. All subjects will be coming in for an overnight confinement to provide 24-hour urine samples at Days 30 (±3 days) and 60 (±3 days).

n. Blood collection for BoE and BoPH assessments; blood collection for COHb will occur on Days -1, 5, Days 30 (±3 days) and 60 (±3 days) and blood collection for CEVal will occur on Days -1 (baseline), 30 (±3 days) and 60 (±3 days). All blood collection for BoE and BoPH will occur at 21:30 (+/- 30 minutes). Blood collected on Day -1, Day 5, and on first day check-in for an overnight confinement for Day 30 (+/- 3 days) and Day 60 (+/- 3 days) will be used for BoPH analysis.

o. An mCEQ for cigarettes for continue to smoke arms and HTP arms will be administered in the afternoon during confinement on Days -1. Starting on confinement Days 3 and 5, product specific mCEQ for continue to smoke arms and HTP arms (mCEQ and mCEQ-HTP respectively) will be administered in the afternoon. During an ambulatory phase, a product specific mCEQ will be administered in the afternoon of the day subject checks in for overnight confinements for Day 30 (+/- 3 days) and Day 60 (+/- 3 days).

p. Subjects in HTP arms will have product accountability performed at all return visits. Product accountability will take place on the same day subjects check-in on for Day 30 (+/-3 days) and Day 60 (+/- 3 days).

q. Study compliance assessment will be performed at each return visits based on arm assignment; HTP arms will be assessed for average HTS used per day, study compliance, and other tobacco product use; Continue Smoking arms will be assessed for average cigarettes per day, study compliance, and other tobacco product use; Smoking Abstinence arm will be assessed for study compliance and other tobacco product use.

r. For the 24-hour urine collection on Day 30 (±3 days) and Day 60 (± 3 days), the overnight confinement will start on Day 29 (±3 days) and Day 59 (±3 days).

s. Principal Investigator will provide tobacco cessation information at screening and at the end of the study or early termination by providing subjects with QuitAssist® website (using information cards, subject handouts, etc.).

t. End of study or early termination procedure will include physical examination, check of vital signs, adverse experience assessment, spirometry, and urine/serum pregnancy test.

u. Expired carbon monoxide (eCO) assessment will be done at screening and at Days 15, 30, 45 and 60 during an ambulatory phase. On Days 30 (+/- 3 days) and 60 (+/- 3 days), eCO will be assessed when subjects check in for overnight confinement for 24-hour urine collection.

v. Subject disposition status will be documented at the end of confinement (Day 6) and at end of the study (Day 60)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
4-ABP	4-aminobiphenyl
1-AN	1-aminonaphthalene
2-AN	2-aminonaphthalene
AE	adverse experience
ALCS	Altria Client Services LLC
ATS	American Thoracic Society
AS	adult smoker(s)
BoE	biomarker of exposure
CEMA	cyanoethylmercapturic acid
CEVaL	N-(2-cyanoethyl) valine
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
COHb	carboxyhemoglobin
CPD	number of cigarettes smoked per day
CRO	contract research organization
CV	coefficient of variation
DMP	Data Management Plan
ECG	electrocardiogram
eCRF	electronic case report form
eCO	Expired carbon monoxide
EDC	electronic data capture
EOS	end of study
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FTCD	Fagerström Test for Cigarette Dependence
FVC	forced vital capacity
GCP	good clinical practice
HEMA	2-hydroxyethyl mercapturic acid
HPHC	harmful and potentially harmful constituent
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
3-HPMA	3-hydroxypropylmercapturic acid
HTP	Heated Tobacco Product

HTS	Heated Tobacco Stick
HTSPD	number of heated tobacco sticks used per day
ICF	informed consent form
ICH	International Council for/Conference on Harmonization
IRB	institutional review board
LSM	least-squares means
3-OH-B[a]P	3-hydroxybenzo[a]pyrene
MedDRA	Medical Dictionary for Regulatory Activities
mCEQ	Modified Cigarette Effects Questionnaire
NE	nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNN	N'-Nitrosonornicotine
QA	quality assurance
QTcF	QT interval corrected for heart rate using Fridericia's method
RCT	Randomized Clinical Trials
S-BMA	S-benzyl mercapturic acid
SPMA	S-phenyl mercapturic acid
SAE	serious adverse experience
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of mean
UBCC	usual brand combustible cigarette
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Background

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 (WHO, 2021, OSH, 2014, Hatsukami et al., 2007). The U.S. Food and Drug Administration ("FDA"), through its "Comprehensive Strategy" for regulating tobacco products (FDA, 2022), and Altria, through its 10-Year Vision, are pursuing efforts to reduce individual and population harms by encouraging adult smokers, 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.

There have been several systematic reviews published on heated tobacco products that are currently available in international markets (Drovandi et al., 2020, Akiyama et al., 2021, and Malt et al., 2022), where the authors reviewed randomized controlled trials (RCT) on exposure to the harmful and potentially harmful chemicals (HPHCs) and related BoE generated from HTPs compared to combustible cigarettes in adult smokers. These reviews highlight that HTPs produce significantly simpler aerosols than combustible cigarettes and significantly lower levels of HPHC in aerosols as measured BoE in adult smokers (Malt et al., 2022). Furthermore, in most cases, the exposures to HPHCs were similar to adult smokers who abstained from smoking with exception of nicotine and couple of tobacco specific nitrosamines (TSNAs) (Drovandi et al., 2020). In addition, a systematic review of 25 RCTs with various HTPs, and adverse health effects, the authors reported marked improvements in clinically relevant BoPHs levels compared to persistent smokers and concluded HPTs have the potential to reduce the risk of chronic diseases in adult smokers (Zynk et al., 2021).

Ploom heated tobacco products (HTPs) are part of the non-combustible tobacco product categories and the Ploom HTP used in this study is a prototype that is not marked in the US. The HTP heats a heated tobacco stick (HTS) at lower temperatures without combustion, to produce an aerosol containing nicotine. The results of chemical analyses of the aerosols generated by such HTPs consistently show that most of the measured selected cigarette smoke constituents, such as HPHCs, were significantly lower than those found in combustible cigarettes (Takahasi et al., 2018, Jaccard et al., 2017, Forster et al., 2018).

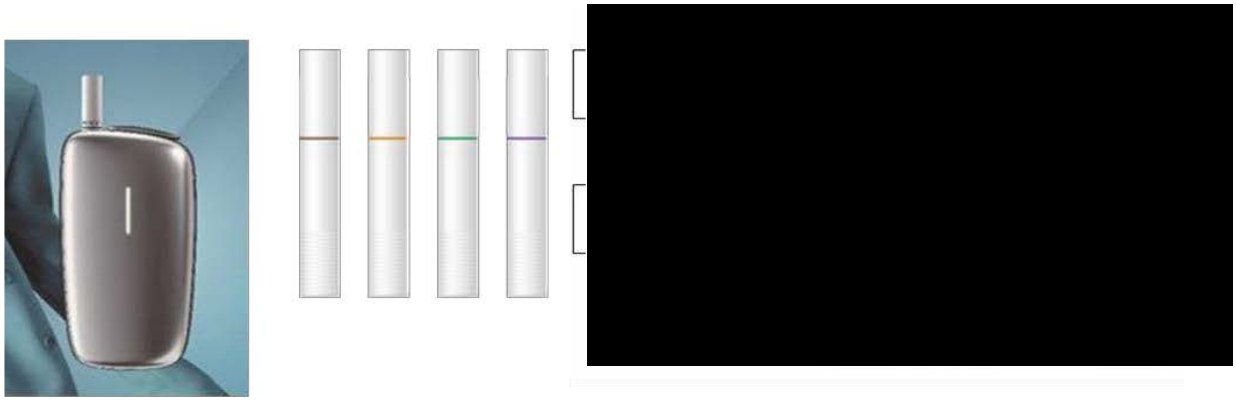
While there are no published data on current study product, two recent studies conducted by Yuki et al. (Yuki et al., 2018 and Yuki et al., 2022) using earlier versions of Ploom brand of HTPs showed that BoE values were significantly reduced compared to combustible cigarette users in a 5-day confinement 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 subjects who abstained from smoking.

1.2. Study Product Background

1.2.1. Test Product

The test product is a heated tobacco product (HTP) intended for adult smokers as an alternative to combustible cigarettes. The Ploom HTP consists of a durable hand-held battery-operated device (Figure 1) and a disposable tobacco-containing stick that is inserted into the device (Figure 1). The stick consists of [redacted] pon activation of the device by inserting an HTS, the device will heat the tobacco in the HTS in a controlled manner to an operating temperature and will generate an inhalable aerosol without burning the tobacco stick.

Figure 1: Heated Tobacco Product



A: Device **B: Tobacco Sticks** **C: Cut-away View of Assembled HTP**

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

1.2.2. Comparator Product

For comparison of biomarkers of exposure from use of HTS, subjects enrolled in the Continue Smoking arms will use their UBCC throughout the study.

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 heated tobacco sticks (HTS) and a market leading cigarette in Japan; 51 constituents (HPHCs and metals) were assessed under controlled conditions (modified Health Canada Intense (mHCI) regimen, 55ml 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 heated tobacco sticks 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] This is lower than the temperature needed for combustion to take place. In comparison, similar HTP products such as IQOS and glo have maximum temperatures ranging from approximately 250°C (glo Hyper and glo Pro) to 350°C (IQOS).

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), that 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 subjects assigned to Continue smoking arms 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.

1.5. Study Rationale

The association between cigarette smoking and the risk of developing chronic diseases, such as respiratory and cardiovascular diseases and cancer in various organ systems have been well established (2014 US Surgeon General Report – The Health Consequences of Smoking). However, the individual risk of developing any of the disease states vary with duration, intensity of smoking, age, in addition to more complex relationships between the excess relative risk and duration and intensity of smoking.

Tobacco smoke contains more than 7,000 chemicals, of which, at least 250 are classified as chemicals or chemical compounds that cause or could cause harm to smokers or nonsmokers that are known as HPHCs (HHS 2010, HHS 2014, HHS 2016). The FDA has also established a list of 93 HPHCs in tobacco products and tobacco smoke (FDA, 2012). This study aims to demonstrate a reduction in exposure to selected HPHCs and to evaluate the exposure to selected HPHCs that are on the priority list of toxic contents and emissions of tobacco products (WHO, 2018, FDA, 2012) in adult smokers switching to Ploom HTPs via assessment of BoE, which is defined as a "tobacco constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose" (IOM, 2012), both in confinement and in the real-world (ambulatory) setting.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The following objectives will be evaluated in each study group.

2.1.1. Primary Objective

- To compare urinary and blood BoEs between HTP arms and the corresponding Continue Smoking arm following 5 days of *ad libitum* use of HTPs or cigarettes in a confinement setting.

2.1.2. Secondary Objectives

- To compare changes in urinary and blood BoEs between baseline and Day 5 (following 5 days of *ad libitum* use in a confinement setting) and Day 60 (±3 days; following 55 days of *ad libitum* use in an ambulatory setting) in the HTP arms and the corresponding Continue Smoking and Smoking Abstinence arms.
- To compare changes in urinary and blood BoEs between the HTP arms and the corresponding Continue Smoking arm following 5 days of *ad libitum* use in a confinement setting and following 55 days of *ad libitum* use in an ambulatory setting.
- To assess subjective effects in the HTP arms compared to corresponding Continue Smoking arm following *ad libitum* use in confinement and ambulatory settings.
- To compare changes in urinary and blood BoPHs between the HTP arms and the corresponding Continue Smoking and Smoking Abstinence arms following 5 days of *ad libitum* use in a confinement setting and following 55 days of *ad libitum* use in an ambulatory setting.
- To characterize use of HTPs during the 5-day confinement period and the 55-day ambulatory period.
- To confirm the safety of Ploom HTPs during a 60-day use period.

2.1.3. Exploratory Objective

- To assess respiratory symptoms experienced while using the Ploom HTPs over 60 days.

2.2. Endpoints

2.2.1. Primary Endpoints

The primary BoEs are presented in Table 1.

Table 1: Primary Biomarkers of Exposure

Biomarker of Exposure	Abbreviation	Associated Toxicant	Matrix
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	NNAL	4-(methylnitrosoamino)-1-(3-pyridinyl)-1-butanone	Urine (24-hour)
Total N'-Nitrosonornicotine	NNN	N'-Nitrosonornicotine	Urine (24-hour)
2-hydroxybutenyl mercapturic acid	2-MHBMA	1,3 butadiene	Urine (24-hour)
3-hydroxypropyl mercapturic acid	3-HPMA	Acrolein	Urine (24-hour)
S-phenyl mercapturic acid	SPMA	Benzene	Urine (24-hour)
2 hydroxyethyl mercapturic acid	HEMA	Ethylene oxide	Urine (24-hour)
1-amino-naphthalene	1-AN	1 amino-naphthalene	Urine (24-hour)
2-amino-naphthalene	2-AN	2 amino-naphthalene	Urine (24-hour)
2-cyanoethyl mercapturic acid	CEMA	Acrylonitrile	Urine (24-hour)
3-hydroxybenzo[a]pyrene	3-OH-B[a]P	Benzo-a-pyrene	Urine (24-hour)
3-hydroxy-1-methylpropyl mercapturic acid	HMPMA	Crotonaldehyde	Urine (24-hour)
4-aminobiphenyl	4-ABP	4-aminobiphenyl	Urine (24-hour)
S-benzyl mercapturic acid	SBMA	Toluene	Urine (24-hour)
Carboxyhemoglobin	COHb	Carbon monoxide	Blood

Note: Please refer to the Schedule of Activities for specific blood draw times for collection of BoE in blood

2.2.2. Secondary Endpoints

- The secondary BoEs are presented in Table 2.
- Subjective assessments (mCEQ) among subjects in both HTP and Continue Smoking arms during confinement and ambulatory phases.
- The BoPH are presented in Table 3.
- Daily product consumption from Day 1 to Day 5 (ie, number of cigarettes smoked per day and number of HTS used per day [HTSPD]).
- Daily product consumption (self-reported) from Day 6 to Day 60 (±3 days) at Day 15 (±3 days), 30 (±3 days), 45 (±3 days), and 60 (±3 days) visits (ie, number of cigarettes smoked per day and average number of HTS used per day) via product accountability and study compliance assessment by site staff.
    - Product accountability will occur for HTP arms only. Number of cigarettes used for the continue to smoke arms will be based on self-reports.
    - Subjects in HTP arms will return any partially used packs and unused packs of HTS they have used during the preceding weeks to the site for accountability on ambulatory visits (Day 15, 30, 45 and 60). Once accountability is completed, site staff can discard partially used packs
- Safety assessments: Adverse experiences, symptom-driven physical examinations as needed, clinical laboratories as needed, and spirometry.

Table 2: Secondary Biomarkers of Exposure

Biomarker of Exposure	Abbreviation	Associated Toxicant	Matrix
Nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates)	NE	Nicotine	Urine (24-hour)
N-(2-cyanoethyl) valine	CEVal	N-(2-cyanoethyl) valine	Blood (whole)

Table 3: Biomarkers of Potential Harm

Biomarker of Potential Harm	Abbreviation	Matrix
Soluble intercellular adhesion molecule-1	sICAM-1	Blood (whole)
Total white blood cell count	WBC	Blood (whole)
High density lipoprotein cholesterol	HDL-C	Blood (whole)
11-dehydrothromboxane B2	11-DTX-B2	Urine (24-hour)
8-Epi-prostaglandin F2alpha	8-epi-PGF2a	Urine (24-hour)

2.2.3. Exploratory Endpoints

- Respiratory Symptom Experience Scale assessments at Day -1, Day 30 (±3 days), and Day 60 (±3 days).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a multi-site, open-label, two-group (menthol and non-menthol), six-arm (HTP, Continue Smoking, and Smoking Abstinence arms within each group) randomized, clinical study to evaluate changes in BoEs in adult smokers who remain smoking, switch to the Ploom HTP, or abstain from smoking, for 60 days (5 days in clinic followed by 55-day ambulatory phase). This study follows the recommendations of the FDA's final Premarket Tobacco Product Application guidance (FDA, 2023).

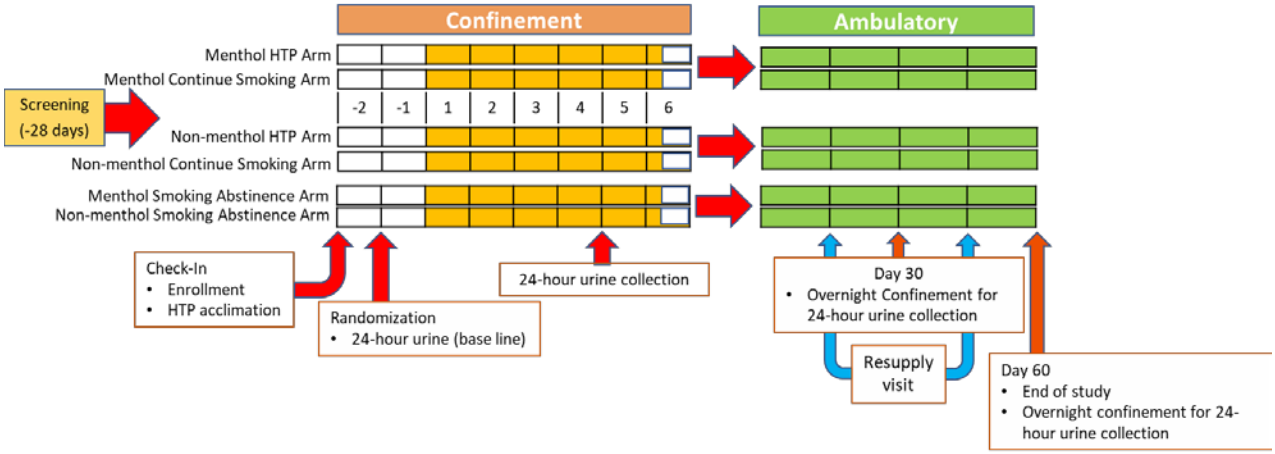
Study population will be divided into 2 groups and within each group, subjects will be randomized into one of 3 arms:

- For Menthol Group:
  - Ploom HTP Menthol HTS arm (n = 60): Subjects will exclusively use the assigned product at least 5 times per day *ad libitum* starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days).
  - Continue Smoking arm (n = 60): Subjects will exclusively smoke their usual brand of menthol cigarettes *ad libitum* starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days). There is no minimum required CPD.
  - Smoking Abstinence Arm (n=30): Menthol smokers will refrain from smoking or use of any tobacco/nicotine-containing products for the entire duration of the study, starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days).
- For Non-menthol Group:
  - Ploom HTP Tobacco HTS arm 2 (n = 60): Subjects will exclusively use the assigned product at least 5 times per day *ad libitum* starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days).
  - Continue Smoking arm (n = 60): Subjects will exclusively smoke their usual brand of non-menthol cigarettes *ad libitum* starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days). There is no minimum required CPD.
  - Smoking Abstinence Arm (n=30): Non-menthol smokers will refrain from smoking or use of any tobacco/nicotine-containing products for the entire duration of the study, starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days).

The goal is to recruit and enroll 300 subjects in total (every attempt will be made to enroll no more than 60% of either gender in each arm) with the aim of obtaining at least 50 completers in each of the HTP and Continue Smoking arms within each group (menthol and non-menthol groups) for the confinement phase. There is no per protocol completers requirement for the Smoking Abstinence arms.

An overview of the study design is shown in Figure 2.

Figure 2: Study Schematic



Abbreviations: HTP = Heated Tobacco Products.

Confinement Phase:

- Day -2: Check-in, enrollment, HTP Product Trial and *ad libitum* use of UBCC.
- Day -1: Randomization; Start 24-hour urine collection (baseline).
- Day 1: Begin using Ploom HTP, begin smoking UBCC, or begin smoking abstinence until Day 5.
- Day 5: Start 24-hour urine collection (end of confinement)

Ambulatory Phase:

- Day 15 (±3 days): Study procedures and Ploom HTS resupply visit
- Day 29 (±3 days): Confinement starting on Day 29 to collect 24-hour urine and for other study procedures; Ploom HTS resupply on Day 30 (±3 days)
- Day 45 (±3 days): Study procedures and Ploom HTS resupply visit
- Day 59 (±3 days): Confinement starting on Day 59 to collect 24-hour urine and for other study procedures

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to check-in on Day -2. Subjects will be admitted into the study site on Day -2 and will be confined to the study site until discharge on Day 6.

The total duration of study participation for each subject (from screening through last visit) is anticipated to be approximately 12 weeks.

The start of the study is defined as the date the first subject signs an informed consent form (ICF). The point of enrollment occurs at the time of subject check-in visit (Day -2). The study completion is defined as the date of the last subject's last assessment (scheduled or unscheduled). Subjects will not be forced to use the tobacco/nicotine products at any time during the study.

See the Schedule of Activities for more details.

3.2. Selection of Study Products

Ploom HTPs are available in Tobacco and Menthol flavors. As HTPs generate substantially less HPHCs than combustible cigarettes, one representative HTS from each flavor category were chosen following a review of HPHC data from each HTS to provide the robust exposure data. Subjects in the HTP arms will be required to use at least 5 HTPs per day, to ensure adequate use of the product and subsequent exposure to HPHCs.

3.3. Study Events and Procedures

3.3.1. Screening

Screening will be performed within 28 days of prior to check-in (Day -2). Medical and tobacco use histories, demographic data will be collected. Other screening procedures include a physical examination, vital signs, ECG, spirometry assessment, weight, height, and BMI, clinical laboratory assessments (hematology, serum chemistry, serology), routine urinalysis, urine/saliva drug screen, urine/breath alcohol screen, urine cotinine screen, and serum pregnancy testing and FSH assessment (for females as age and symptom appropriate). In addition, Principal Investigator will provide tobacco cessation information and QuitAssist® website at screening. Subjects may be re-screened upon sponsor approval.

3.3.2. Check-in and Product Trial

After completing check-in procedures on Day -2, subjects will have an opportunity to try HTP study product variants (menthol or tobacco HTS) based on their UBCC before being randomized. The Product Trial will consist of use of a single menthol or tobacco HTS. Following the Product Trial session, all subjects will smoke their UBCC until 23:00 on Day -2 and from 07:00 to 23:00 on Day -1.

3.3.3. Randomization

Day -1: Subjects will be assigned to either a menthol or a non-menthol group based on their UBCC flavor category. Following group assignment, subjects will be randomized to one of the three arms based on gender and CPD stratification use (Low </= 16, or High > 16). The three arms are: Ploom HTP, continued cigarette smoking (Continue Smoking), and Smoking Abstinence arms in a 2:2:1 ratio. Randomization will occur in the afternoon or later on Day-1 to allow product preparation for Day 1 product dispensing. However, participants will not be notified of which arm they are randomized to until Day 1.

3.3.4. Baseline Biological Sample Collection

Baseline 24-hour urine collection will start on the morning of Day -1 and end on the morning of Day 1, which will serve as a baseline 24-hour urinary BoE and BoPH assessment sample.

Blood collection for BoE and BoPH will be done at 21:30 (+/- 30 minutes), starting on Day -1 and 5 during confinement; and on the day subjects check in for overnight ambulatory visits for Day 30 (+/- 3 days) and Day 60 (+/- 3 days) .

- COHb will be assessed from blood samples collected on Days -1 (baseline), 5, 30 (±3 days) and 60 (±3 days) and CEVal will be assessed from blood samples collected on Days -1 (baseline), 30 (±3 days) and 60 (±3 days).

- Blood collected on Day -1, 5, Day 30 (+/- 3 days) and Day 60 (+/- 3 days) will be assessed for BoPHs (sICAM-1, WBC, and HDL-C)

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Activities.

3.3.5. Subjective Assessments

Subjects in the Continue Smoking and HTP arms will provide responses to subjective assessments during the study in both confinement and ambulatory phases. On Days -1, 3, 5, 30 (±3 days) and 60 (±3 days), site staff will administer the appropriate mCEQ at approximately mid-day.

Subjects in all arms will provide response to Respiratory Symptom Experience Scale at Day -1, Day 30 (±3 days) and Day 60 (±3 days).

3.3.6. Study Product Use

Subjects who are randomized to HTP arms will begin using the assigned HTS starting on the morning of Day 1 (after completion of the baseline 24-hour urine collection) and continue HTP use through the end of the 60-day ambulatory phase.

3.3.6.1. Day 1 – Day 6 (Confinement Phase)

- Subjects randomized to the HTP arms will use the assigned HTS exclusively (either menthol or tobacco flavor) starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days). At least 5 HTS will be used per day *ad libitum* between the hours of 07:00 through 23:00. Subjects may use product more than the minimum use requirement. Subjects will request one study product at a time from the pharmacy/designated site staff and return the used HTS prior to receiving another HTS.

- Subjects randomized to the Continue Smoking arms will exclusively smoke their UBCCs *ad libitum* from 07:00 through 23:00 starting on the morning of Day 1 (after

completion of baseline urine collection) through Day 60 (±3 days). Subjects will request one cigarette at a time from the pharmacy/designated site staff and return the used butt prior to receiving another cigarette. There is no minimum required CPD.

- Subjects randomized to the Smoking Abstinence arms will abstain from smoking or using any tobacco/nicotine-containing products for the entire duration of the study, starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days).

- Smoking and HTS use will be limited to a designated area of the site. Subjects in HTP arms will use an area separate from subjects in the Continue Smoking arms. Use of HTS or cigarettes will not be permitted from 23:00 to 07:00 each day starting from check-in (Day -2) until the end of confinement (Day 6).

- For product accountability and compliance, all smoked butts and all used HTS will be collected throughout the confinement phase (Day -2 through Day 5). All product uses, CPD, and HTSPD, will be documented. Once site staff has collected used butts and used HTS, site staff will record and reconcile the product dispensed for use and returned. Once reconciliation is completed, all used products (both UBCC and HTS) can be discarded.

3.3.6.2. Day 6 - Day 60 (Ambulatory Phase)

- Subjects who have successfully completed the confinement phase of the study per protocol will continue to the ambulatory phase. Subjects in the HTP arms will be provided a Ploom HTP device and a 2-week supply of HTS based on their consumption during confinement (plus two additional packs of HTS) for use at home until the next scheduled visit.

- Subjects will exclusively use their assigned HTS *ad libitum* (at least 5 HTS per day; HTS arms), smoke their UBCC *ad libitum* (Continue Smoking arms), or continue to abstain from any tobacco/nicotine-containing products (Smoking Abstinence arms) starting from the morning of Day 6 (after discharged from the confinement phase).

- On Days 15 (±3 days) and 45 (±3 days), all subjects (from all 6 arms) will return to the site for study procedures. Subjects in the HTS arms will also receive a resupply of HTS.

    - Product accountability and study compliance assessment will be performed by site staff and replenish subjects with additional HTS for use at home.

    - Product accountability will occur for HTP arms only. Number of cigarettes used for the continue to smoke arms will be based on self-reports.

    - Subjects in HTP arms will return any partially used packs and unused packs of HTS they have used during the preceding weeks to the site for accountability on ambulatory visits. Once accountability is completed, site staff can discard partially used packs

- eCO will be measured for all subjects.
    - eCO > 5 ppm in the HTP or Smoking Abstinence arms will prompt counseling by site staff on the Tobacco and Nicotine Restrictions and protocol compliance will be discussed and reinforced at each return visits.
    - eCO > 8 ppm at two consecutive return visits may cause subject in HTP and Smoking Abstinence arms to be dismissed from the study pending discussion with Principal Investigator and the Sponsor.
    - For all eCO assessments, Principal Investigator can reassess eCO at their discretion to confirm initial eCO value.
- For all subjects, study compliance assessment will be performed by the site staff, non-study tobacco product use as well as average cigarettes used per day for subjects in the Continue Smoking arms.

- On Day 29 (±3 days) and Day 59 (±3 days), all subjects (from all 6 arms) will return to the site and start an overnight confinement for the 24-hour urine collection and other study procedures. Subjects in the HTP arms will receive a resupply of HTS on Day 30 (±3 days) prior to checkout.
    - Subjects will check-in to sites for an overnight confinement visit to provide 24-hour urine samples.
    - eCO will be measured for all subjects, refer to above section for eCO assessment guidance.
    - Product accountability and study compliance assessment by site staff
    - Product accountability will occur for HTP arms only. Number of cigarettes used for the continue to smoke arms will be based on self-reports.
    - Subjects in HTP arms will return any partially used packs and unused packs of HTS they have used during the preceding weeks to the site for accountability on ambulatory visits. Once accountability is completed, site staff can discard partially used packs
    - Replenish subjects with additional HTS for use at home (Day 30 [±3 days] only).
    - Subject will check-in at site and begin 24-hour urine collection that will end at 24 hours from the check-in. Thus, if subject checks-in at site at 1pm, site will collect urine samples for the next 24 hours, including the first morning void.
    - Urine and blood samples will be collected for BoE, BoPH, and biomarkers of compliance at these visits (BoPH Urine on Day 29 and 59, BoPH Blood on Day 59)

- For all subjects, study compliance assessment will be performed by the site staff, non-study tobacco product use as well as average cigarettes used per day for subjects in the Continue Smoking arms.

4. SELECTION OF STUDY POPULATION

Self-affirmed adult smokers will be screened to enroll approximately 300 subjects (every attempt will be made to enroll no more than 60% of either gender in each arm). The study population will be divided into either menthol or non-menthol groups and within each group, subjects will be randomized to one of 3 arms per group as referenced in Section 3.

4.1. Inclusion Criteria

Subjects must satisfy all the following criteria at the screening visit unless otherwise stated:

1. Voluntary consent to participate in this study documented on the signed ICF.
2. Healthy adult males and females ≥ 22 and ≤ 65 years of age, inclusive, at Screening.
3. Smoking history (self-reported at screening) of an average of at least 10 but no more than 30 factory-manufactured combustible cigarettes (either menthol or non-menthol) daily for at least 12 months prior to screening. Brief periods (ie, up to 7 consecutive days) of non-smoking during the 3 months prior to screening (eg, due to illness or participation in a study where smoking was prohibited) will be permitted.
4. Screening and first check-in blood pressure ≤ 150/90 mmHg measured after being seated for at least 10 minutes. Two rechecks may be performed at the Principal Investigator's discretion.
5. Positive urine cotinine (≥ 500 ng/mL) at screening.
6. Exhaled carbon monoxide (eCO) ≥ 10 ppm at screening.
7. Post-bronchodilator forced expired volume in 1 second (FEV1) : forced vital capacity (FVC) ratio > 0.7 and FEV1 > 80% of predicted at screening.
8. Negative pregnancy test at Screening and first check-in (Day -2) for all female subjects.
9. Female subjects who are heterosexually active and of childbearing potential (eg, neither surgically sterile at least 6 months prior to first check-in nor postmenopausal with amenorrhea for at least 12 months prior to first check-in with follicle-stimulating hormone [FSH] levels consistent with postmenopausal status) must have been using one of the following forms of contraception for the time period indicated and agree to continue using it through completion of the study:
   - hormonal (eg, oral, vaginal ring, transdermal patch, implant, injection) consistently for at least 3 months prior to first check-in, when used in combination with male condoms with spermicide (use of NuvaRing® is at the Principal Investigator's discretion)
   - double barrier (eg, condom with spermicide or diaphragm with spermicide) consistently for at least 2 weeks prior to first check-in

- intrauterine device or system (utilize Principal Investigator discretion regarding use of hormonal or nonhormonal devices) for at least 3 months prior to first check-in
- exclusive partner who is clinically sterile (ie, documented infertility or surgical sterilization; see below for additional information on sterility) or has been vasectomized for at least 6 months (inclusive) prior to first 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 subject. Female subjects 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 subjects who are of nonchildbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to first check-in:
    - Hysteroscopic sterilization (including Essure® or similar nonsurgical sterilization procedures);
    - bilateral tubal ligation or bilateral salpingectomy;
    - hysterectomy;
    - bilateral oophorectomy

    Or be postmenopausal with amenorrhea for at least 12 months prior to first check-in and have FSH levels consistent with postmenopausal status.
11. Willing to comply with the requirements of the study.
12. Willing to use Ploom HTP after the Product Trial at first check-in.
13. Willing and able to abstain from cigarettes from Day 1 through the end of the study (EOS) on Day 60 (±3 days) if they are randomized to a Smoking Abstinence arm.

4.2. Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening, first check-in, or prior to randomization, as appropriate.

1. Use of any type of tobacco- or nicotine-containing products other than manufactured cigarettes (eg, e-vapor products, roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) in the 7 days prior to first check-in.
2. Self-reported puffers (ie, adult smokers who draw smoke from the cigarette into the mouth and throat but do not inhale).
3. Planning to quit smoking in the next three months (at screening).
4. History or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, urologic, existing respiratory diseases, immunologic, psychiatric, lymphatic, or cardiovascular disease, or any other

condition that, in the opinion of the Principal Investigator, would jeopardize the safety of the subject or impact the validity of the study results.

5. Clinically significant abnormal findings on the vital signs, physical examination, medical history, ECG, or clinical laboratory results, in the opinion of the Principal Investigator.
6. Positive test for human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus at screening.
7. History or presence of any type of malignant tumors.
8. Current evidence or any history of congestive heart failure.
9. Diabetes mellitus (fasting glucose ≥126 mg/L [7 mmol/L]) that is not controlled by diet/exercise alone, in the opinion of the Principal Investigator.
10. An acute illness (eg, upper respiratory infection, viral infection) requiring treatment with prescribed medicines within 2 weeks prior to first check-in.
11. Any planned surgery from the time of screening through EOS.
12. History of drug or alcohol abuse within 24 months prior to first check-in.
13. Fever (ie, body temperature >100.5°F) at screening or first check-in. One re-check may be performed at the Principal Investigator's discretion.
14. Body mass index greater than 40.0 kg/m^2 or less than 18.0 kg/m^2 at screening.
15. Systolic blood pressure >150 mmHg and/or diastolic blood pressure > 90 mmHg at screening or first check-in, measured after being seated for at least 10 minutes. Two re-checks may be performed at the Principal Investigator's discretion.
16. Estimated creatinine clearance (by Cockcroft-Gault equation) < 80 mL/minute at screening.
17. Serum alanine aminotransferase ≥1.5 times the upper limit of normal and/or aspartate aminotransferase ≥1.5 times the upper limit of normal at screening.
18. Positive screen for alcohol (urine/breath) or any of the following drugs of abuse (urine/saliva), regardless of the reason of use: amphetamines, methamphetamines, opiates, cannabinoids, or cocaine at screening or first check-in.
19. Female subjects who are pregnant (positive serum pregnancy test at screening or urine/serum pregnancy test at first check-in), lactating, or intend to become pregnant from screening through EOS.
20. Use of prescription or over-the-counter bronchodilator medication (eg, inhaled or oral ß-agonists) for treatment of any illnesses and within 12 months prior to first check-in and throughout the study.
21. Use of medications or foods 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, grapefruit, 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 first check-in or during the study.

22. Use of antibiotic treatment within 2 weeks prior to first check-in.
23. Plasma donation within 7 days prior to first check-in.
24. Donation of blood or blood products (with the exception of plasma as noted above), had significant blood loss, or received whole blood or a blood product transfusion within 56 days prior to first check-in.
25. Participation in a previous clinical study for an investigational drug, device, biologic, or a tobacco product within 30 days prior to first check-in.
26. Subject or a first-degree relative (ie, parent, sibling, child, spouse/partner) is a current or former employee of the tobacco industry or a named party or class representative in litigation with any tobacco company.
27. Subject or a first-degree relative (ie, parent, sibling, child, spouse/partner) is a current employee of the study site.
28. Have been diagnosed with major depressive disorder or have a history of suicide attempt.
29. Have pre-bronchodilator to post-bronchodilator FEV1 increases of greater than or equal to 12% or grade “C” or worse per ATS/ERS 2019 standards.

4.3. Subject Number and Identification

Subjects will be assigned a unique subject identification number upon signing informed consent.

Subjects will be identified by subject number on all study documentation.

4.4. Subject Withdrawal and Replacement

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

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

Subjects discontinuing from the study will not be replaced. Subjects enrolled in the Product Trial but failed at first check-in or dropped prior to randomization will not be replaced. Subjects 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 subject
- Death
- Noncompliance with study product or the protocol
- Other (reasons other than the above should be noted)

If a subject is withdrawn from the study, the sponsor will be notified and the date and reason(s) for the withdrawal and withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all EOS assessments (Schedule of Activities). Other procedures may be performed at the Principal Investigator's (or designee's) and/or sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The Principal Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Principal Investigator (or designee) to have stabilized.

4.5. Study Termination

The study may be discontinued at the discretion of the Principal Investigator (or designee), sponsor, or sponsor's medical monitor if any of the following criteria are met:

- Adverse experiences unknown to date (ie, not previously reported in any similar study on the study products with respect to their nature, severity, and/or duration)
- Increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at first check-in as baseline signs and symptoms)
- Medical or ethical reasons affecting the continued performance of the study
- Other administrative reasons.

5. STUDY PRODUCTS

5.1. Description, Storage, Packaging, and Labeling

Study products will be supplied by the sponsor (or designee), along with the batch/lot numbers and certificates of analysis. For product description of HTPs, refer to Section 1.2.1. For description of comparator products, refer to Section 1.2.2.

Details on study products can be found in Sections 1.2.1 and 1.2.2 and in Table 1.

Table 4: Study Products

Study Groups	Study Products/Arms	Route of administration	Test or Reference
Menthol Group	Ploom HTP Menthol HTS; MX3 (681)	INH	Test
	Menthol UBCC	INH	Reference
	Smoking Abstinence	NA	NA
Non-menthol Group	Ploom HTP Tobacco HTS; R8 (120)	INH	Test
	Non-menthol UBCC	INH	Reference
	Smoking Abstinence	NA	NA

The HTS will be provided in a sealed plain pack. Each pack contains 20 tobacco sticks. The tobacco sticks are designed to be used with the Ploom HTP device exclusively and will not work with any other heated tobacco product devices and HTS cannot be used like a combustible cigarette by lighting it.

Heated tobacco sticks will be stored at the study site in a secure location within the pharmacy or in secure location with locked and restricted access.

The study product containers will be labeled in accordance with applicable laws and regulations.

Subjects' UBCC will be provided by the subjects who are randomized to the Continue Smoking arms throughout the study. For the duration of confinement, subjects will provide study sites with sufficient number of un-opened cigarette packs to last the duration of confinement. Subjects will bring a sufficient supply (unopened packs) of their UBCC for personal use at designated times throughout confinement in the site.

5.2. Study Product Administration

5.2.1. Product Trial

At Day -2, following check-in, all subjects will engage in a brief Ploom HTP Product Trial using flavor variants of HTS that matches subject's usual brand of cigarette's flavor category to become accustomed to the product and to confirm their ability to correctly use the study product. Subjects will receive detailed instruction on features of the Ploom HTP devices, including how to turn on the device as well as instructions on how to use the product with the tobacco stick inserted in the device.

5.2.2. Product Use from Day 1 – Day 5

Subjects will begin using the assigned study products or completely stop using tobacco products on the morning of Day 1 and continue through Day 5 according to the randomization:

- Subjects in HTP groups will be required to smoke their assigned HTS at least 5 times per day *ad libitum* from 07:00 through 23:00. Once subjects meet the required minimum

product use, they can request additional products from the pharmacy (ie, there is no maximum limit on HTS use). The pharmacist or designated study staff will dispense one product per request and record product use for each subject in a product accountability log.

- Subjects in Continue Smoking arms will smoke their UBCC *ad libitum* from 07:00 through 23:00. Subjects can request cigarettes from the study staff. The pharmacist or designated study staff will dispense one cigarette per request and record product use for each subject in a product accountability log.
- Subjects in the Smoking Abstinence group will remain abstain from cigarette smoking for the duration of the study during both the confinement and ambulatory phases.

Study product use will not be permitted from 23:00 to 07:00 each day during the study from check-in (Day -2) until Day 6.

5.3. Randomization

As previously noted in Section 3.3.3, subjects will be randomized to one of the following 3 arms in a 2:2:1 ratio, based on their UBCC flavor profile. Subjects will be randomized based on gender CPD stratification use (Low </= 16, or High > 16) based on the cigarettes per day information obtained at the screening visit. Randomization will occur on Day -1. Randomization will occur in the afternoon or later on Day-1 to allow product preparation for Day 1 product dispensing. However, participants will not be notified of which arm they are randomized to until Day 1

Table 5: Group Allocation

Study Group	Study Product	Study Arms	Subjects (n)	Randomization Ratio
Menthol	A	Ploom HTP Menthol HTS; MX3 (681)	60	2
	B	Continue Smoking (menthol)	60	2
	C	Smoking Abstinence (menthol)	30	1
Non-menthol	D	Ploom HTP Tobacco HTS; R8 (120)	60	2
	E	Continue Smoking (non-menthol)	60	2
	F	Smoking Abstinence (non-menthol)	30	1

5.4. Blinding

This is an open-label study.

Study Product Compliance

5.4.1. Product Compliance During Confinement (Day -2 to Day 6)

During confinement, all smoked cigarette butts and all used HTS will be collected (from Day -2 to Day 5).

The following measures will be employed to ensure study product use compliance:

- During confinement, subjects in HTP groups will request HTS from the pharmacy or a designated clinic staff each time they want to use a HTS. Subjects are required to use a minimum of 5 HTS between 07:00 and 23:00. Additional products can be requested if subjects desire to use more HTS. One Ploom device and one HTS will be dispensed per request. Subjects will be instructed to return each used Ploom HTP (device and HTS) upon completion.
- Subjects in Continue Smoking arms will request a cigarette from the clinic staff each time they want to smoke a cigarette. They will be instructed to return each cigarette butt upon completion. Only 1 cigarette will be dispensed for use at a time and subjects will be instructed to return the cigarette butt before being allowed to obtain another cigarette.
- Site will collect used butts and HTS during confinement. Site staff will record and reconcile the product dispensed for use and returned. Once reconciliation is completed, all used products (both UBCC and HTS) can be discarded.

5.4.2. Product Compliance During Ambulatory Phase (Day 6 to Day 60 [±3 days])

- Upon completion of the confinement phase (Days -2 to morning of Day 6), subjects from HTP groups will be discharged to home with one Ploom HTP device and sufficient HTS (20 HTS per pack) for exclusive use of HTS at home until their next scheduled visit on Day 15 (±3 days). During return visits on Days 15 (±3 days), 30 (±3 days), and 45 (±3 days), subjects will return used HTS packs and be given additional tobacco sticks for use at home based on their HTSPD from previous visit. At any time, subjects can request additional HTS from clinic if they run out of the HTS received at the previous visit.
- Subjects in the Continue Smoking arms will smoke their UBCC as normal.
- Product compliance for HTP arms will be done via product accountability and study compliance assessment by site staff and will capture study compliance, non-study tobacco product use if any.
- Subjects in HTP arms will return any partially used packs and unused packs of HTS they have used during the preceding weeks to the site for accountability on ambulatory visits (Day 15, 30, 45 and 60). Once accountability is completed, site staff can discard partially used packs
- For subjects in the Continue Smoking arms, study compliance assessment by site staff will capture self-reported average cigarettes per day and study compliance. Subjects are not required to bring back used cigarette butts on return visits for product accountability.
- For subjects in Smoking Abstinence arms, study compliance assessment by site staff will capture study compliance, non-study tobacco product use if any.
    - Additional product compliance will be assessed with eCO at all return visits and CEMA and CEVal will be assessed on Days 30 (±3 days) and 60 (±3 days) with 24-hour urine and blood draw respectively for all subjects.

5.5. Study Product Accountability, Storage, and Preparation

All study products will be provided by the sponsor, except UBCCs. The study staff at the site will coordinate shipping of the study products from the sponsor. The study staff will

document the date each shipment was received and record it in the inventory records. The study 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 EOS. The site pharmacy will retain and store 2 packs of each study product at the site until finalization of the final study report.

All subjects will be required to provide a sufficient supply of their UBCC to the study site for use from check-in (Day -2) through Day 6 (8 days) in case they are randomized to the Continue Smoking arms and continue to smoke their UBCC. This supply will be calculated from the number of CPD reported at screening plus an additional 20% rounded up to the next pack. For example, a subject reporting to smoke 15 CPD would bring 9 packs (15 CPD x 10 days = 150 cigarettes + an additional 30 cigarettes = 180 cigarettes total [9 packs]). The clinical site will purchase additional cigarettes if subjects run out of cigarettes during the study.

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

For study subjects randomized to continue smoking, any unused packs of cigarettes will be returned to them upon their completion of confinement (Day 6 at check-out). For the study subjects randomized to Ploom HTP or Smoking Abstinence, any unused packs of cigarettes will be returned to them upon their completion (Day 60) or withdrawal from the study.

Upon completion of the study, when approved by the sponsor all remaining study product (with exception of the retained study product) will be sent back/destroyed using the following methods:

- Ploom HTP devices: will be sent to back to the sponsor upon completion of the study.
- Ploom Menthol and Tobacco HTS: sticks will be rendered unusable by site staff by breaking sticks in half, soaking them in water, and disposing of them in the regular trash.

Sites will document amounts and dates of shipping/destruction on the Master Product Accountability Forms. Throughout the study after accountability is completed partially used packs may be discarded using the method listed above for HTS once accountability has been completed.

6. CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

6.1. Concomitant Medications

Any medications, and the reason for its use, taken from 30 days prior to first check-in through check-in will be recorded as prior medications.

Any concomitant medications, and the reason for its use, taken from first check-in through the EOS (or upon early termination) will be recorded as concomitant medication.

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

Stable doses (ie, no dosage adjustments within 30 days prior to check-in) of prescription or over-the-counter medications required to treat a Principal Investigator-approved disease or condition are permitted at the discretion of the Principal Investigator. Hormonal contraceptives (eg, oral, vaginal ring, transdermal patch, implant, injection) and hormonal replacement therapy are permitted. Use of over-the-counter analgesics (eg, acetaminophen, ibuprofen), milk-of-magnesia, antihistamines, and nasal decongestants are permitted as needed to treat AEs experienced by subjects, at the discretion of the Principal Investigator. Note that some decongestants might cause a positive urine/saliva drug screen result and therefore their use should be discouraged within 5 to 7 days of those tests.

The administration of any other concomitant medications during the study is prohibited without prior approval of the Principal Investigator (or designee), unless its use is deemed necessary for the treatment of an AE.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study related activities.

No foods or beverages containing alcohol, and poppy seeds should be avoided for 48 hours prior to Screening and first check-in to avoid exclusion criteria for a positive drug test and throughout the study.

In addition, consumption of broiled or pan-fried meat, pre-cooked meats (eg, tuna, ham, corned beef, smoked lunchmeats), bacon, eggplant or sausage will not be allowed for 48 hours prior to first check-in, prior to overnight confinements for 24-hour urine collection on Days 29 (±3 days) and 59 (±3 days), and during the confinement at the study site. Every attempt will be made to ensure that food provided to a subject on Day -1 is similar to what is provided to that subject on Day 5 as well as on the first day of confinement for visits at Day 29 (±3 days) and Day 59 (±3 days). Similarly, the food provided to a subject on Day 1 is similar to what is provided to that subject on Day 6 as well as on the second day of confinement for visits at Day 30 (±3 days), and Day 60 (±3 days).

Caffeinated beverages (up to 1 cup per meal) may be served while subjects are confined at the study site.

Subjects will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations at screening.

6.3. Smoking and HTP use

Following Product Trial on Day -2, all subjects will continue to smoke their UBCC through 23:00 and from 07:00 to 23:00 on Day -1.

Starting on the morning of Day 1, subjects in HTP arms will be required to use the Ploom HTP HTS exclusively until the EOS (Day 60 [±3 days]). Subjects in HTP arms will not be allowed to smoke any tobacco- or nicotine-containing products until EOS (Day 60 [±3 days]).

Subjects in Continue Smoking arms will be allowed to smoke their UBCC throughout the study without any restrictions.

Smoking and HTP use will be limited to a designated area of the clinic. Subjects in HTP arms will use an area separate from subjects in the Continue Smoking arms.

Any illicit use of any tobacco- or nicotine-containing products or sharing of study products will be strictly prohibited and will be grounds for immediate termination from the study at the discretion of the Principal Investigator.

6.4. Exercise

Strenuous exercise will be forbidden for 48 hours prior to check-in and while the subject is confined at the study site.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- 24-hour urine collection
- Subjective effects questionnaire
- Vital signs
- ECG
- Physical examination including an oral exam
- Blood samples.

7.1. Biomarker of Exposure and Potential Harm Assessments

7.1.1. Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Activities.

Procedures for collection, processing, and shipping of blood samples will be detailed in a separate document.

The maximum blood volume for the entire study, including samples taken for safety evaluation, will not exceed 450 mL.

7.1.1.1. Analytical Methodology

Blood concentrations of COHb, CEVal, sICAM-1, WBC, and HDL-C will be determined using validated analytical procedures. Specifics of the analytical method will be provided to the sponsor as a separate document.

7.1.1.2. Biomarker Assessments

BoEs and BoPH that are present in the blood will be assessed from blood collected at specific timepoints (see BoEs listed in Table 1 and Table 2, BoPH listed in Table 3 and Schedule of Activities).

Blood samples for COHb and CEVal will be collected in the evening at approximately 21:30 (+/- 30 minutes) on study days per schedule of activities.

7.1.2. Urine Sample Collection and Processing

A 24-hour urine collection will be performed at the times indicated in the Schedule of Activities.

All urine voids will be collected over each 24-hour collection period (24-hour urine) for BoE analysis. During the confinement period Day -2 through Day 6, the 24-hour urine collection will begin at 07:00 (± 30 minutes) pn Day -1 (baseline) and Day 5, and finishes the following morning at 07:00 (± 30 minutes) on Day 1 and Day 6. During overnight confinement in the ambulatory period Day 30 (±3 days) and Day 60 (±3 days), the 24-hour urine collection will begin following check-in (± 30 minutes). For further 24-hour urine collection procedures please refer to the Sample Handling Manual.

Unused urine samples will be frozen and may be used for additional biomarker assessments for up to 3 years.

Procedures for collection, processing, and shipping of urine samples will be detailed in a separate document.

7.1.2.1. Analytical Methodology

Urinary concentration of BoEs and BoPHs will also be determined using validated analytical procedures (see Table 1, Table 2, and Table 3). Specifics of the analytical method will be provided in a separate document. Urine creatinine will be measured in each 24-hour collection and be used to adjust the concentration values.

7.1.2.2. Biomarker Assessments

BoE and BoPH that are present in the urine will be assessed from 24-hour urine collected as specified in the Schedule of Activities.

7.1.3. Compliance BoE

Biomarker of compliance will be collected during the ambulatory phase on day 15, 30 (±3 days), 45 and Day 60 (±3 days).

- eCO:
  - eCO will be assessed at ambulatory visits on Days 15 and 45 when subjects present to the site.
  - eCO assessment will occur on the day of check-in for overnight confinement for 24-hour urine collection on Day 30 (+/- 3 days) and Day 60 (+/- 3 days).
- CEMA
  - 24-hour urine collected on Day 30 (+/- 3 days) and Day 60 (+/- 3 days) will be used to quantify urinary levels of CEMA.
- CEVal
  - Blood samples will be collected at 21:30 (+/- 30 minutes) on the day of check-in for overnight confinement for 24-hour urine collection on Day 30 (+/- 3 days) and Day 60 (+/- 3 days) for assessment of CEVal.

7.2. Daily Product Consumption

The following parameters will be collected to assess daily product consumption in confinement:

- CPD: number of cigarettes smoked from 07:00 to 23:00, each day
- HTSPD: number of HTP used from 07:00 to 23:00, each day
- Average HTS daily consumption information for HTP arms will be collected via product accountability and study compliance assessment during ambulatory phase.
- CPD information will be collected for both comparator groups (Continue Smoking and Smoking Abstinence) will be collected by study compliance assessment during the ambulatory phase.

7.3. Respiratory Symptom Experience Scale

The Respiratory Symptom Experience Scale (Appendix 5) will be completed at the scheduled timepoints as indicated in the Schedule of Activities.

7.4. Safety Assessments

7.4.1. Adverse Experiences

Adverse Experience definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study.

Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of study product until study completion. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with a Principal Investigator’s (or designee’s) opinion of the relationship to the use of the study product.

Adverse experiences recorded during the course of the study will be followed up, where possible, to resolution or until the unresolved AEs are judged by the Principal Investigator (or designee) to have stabilized. This will be completed at the Principal Investigator’s (or designee’s) discretion.

7.4.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Activities. Clinical laboratory evaluations are listed in Appendix 2.

Subjects will be asked to provide urine/saliva samples for drugs of abuse screen and urine for cotinine test. Alcohol levels may be assessed via urine or breath test depending on the availability of testing methods available to sites at the times indicated in the Schedule of Activities. For female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Activities.

All clinical laboratory tests will be conducted by a laboratory accredited by Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments [CLIA] of 1988) or at the clinical study site using CLIA-waived kits or procedures.

A Principal Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

Values for the laboratory parameters are to be within the laboratory normal ranges or deemed not clinically significant in the opinion of the Principal Investigator (or designee) or otherwise meet the specified values (ranges) in the protocol. One recheck may be performed at the Principal Investigator's discretion for all clinical laboratory tests except for the urine/saliva drug screen, urine/breath alcohol screen, and urine cotinine test.

7.4.3. Vital Signs

Seated blood pressure, seated heart rate, seated respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Activities. Vital signs may also be performed at other times if judged to be clinically appropriate.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Subjects must be seated for at least 10 minutes before blood pressure, heart rate, and respiratory rate measurements.

Product use is to be stopped 15 minutes prior to vital sign measurement.

7.4.4. 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes and at least 15 minutes after the last nicotine containing product used. The ECGs will be performed at the times indicated in the Schedule of Activities. The ECGs will be documented by the Principal Investigator or his/her medically qualified designee as normal, having a clinically insignificant abnormality, or having a clinically significant abnormality.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate. The Principal Investigator (or designee) will perform a clinical interpretation of each 12-lead ECG.

7.4.5. Physical Examination

A general physical examination with observations and questioning by the Principal Investigator or his/her medically qualified designee will be performed at screening. All 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 examination will be performed at the other timepoints specified in the Schedule of Activities.

7.4.6. Spirometry Tests

A spirometry assessment, both pre- and post-administration of a short-acting bronchodilator, will be performed at Screening in accordance with procedures of the American Thoracic Society/European Respiratory Society (Graham et al., 2019). Spirometry without administration of a bronchodilator will be performed at Day 60 (±3 days) or in case of early termination from the study. Spirometry predicted values will be standardized to the Global Lungs Initiative predictive set (Quanjer et al., 2013).

All subjects will be given a pre-test spirometry training using GoClinic app and an opportunity to familiarize themselves with the spirometry equipment and procedures prior to actual spirometry assessment at screening.

Per ATS/ERS 2019 standard, subjects with grade "B" or better (grade A) will be acceptable to participate in the study. Per ATS/ERS 2019 standard, both pre and post bronchodilator testing can be repeated up to 8 times in attempt to gain a satisfactory grading.

The Principal Investigator or their appropriately qualified designee will review the spirometry assessment at Screening as part of the safety assessment. Per Principal investigator's discretion, if screening spirometry results are sub-optimal and subject is within the screening window, PI can repeat spirometry assessment in an unscheduled visit prior to check-in on Day -2. Subject that sub-optimal spirometry results at screening visit and is outside the 28-day screening window, may be eligible for to re-screen at PI discretion and Sponsor approval.

Only subjects with no clinically significant findings will be enrolled onto the study (exclude subjects with pre-bronchodilator to post-bronchodilator FEV1 increases of greater than or equal to 12%).

7.4.7. Support for the Smoking Abstinence Arm

All subjects in the Smoking Abstinence arm will be closely monitored by the site staff from Day 1 until discharged from study at Day 60 (±3 days), or until early termination either voluntarily or by the Principal Investigator for possible signs and symptoms of nicotine withdrawal. This includes clinical monitoring of subject's behavior, mood and any AEs. If a subject shows withdrawal symptoms or experiences any change in their behavior, mood or AEs due to smoking abstinence, the Principal Investigator or designee may consult the medical monitor and the sponsor for appropriate course of action or treatment. In addition, to help alleviate cravings, hard candy will be made available to subjects until 23:00 on each day of confinement.

7.4.8. Tobacco Cessation Information

The Principal Investigator (or designee), at screening and at the EOS or upon early termination, will advise all adult tobacco product users that to reduce the health effects of tobacco, the best thing to do is to quit. The Principal Investigator (or designee) will refer all adult tobacco product users to the QuitAssist® website (using information cards, subject handouts, etc.), which contains citations to a number of third-party information sources, including websites, telephone resources, and other organizations with additional information.

8. SAMPLE SIZE AND DATA ANALYSIS

Full details of the statistical analysis methods for the study will be specified in the SAP.

In general, descriptive statistics will be provided for all analysis variables by study arm and timepoint. The number of subjects with non-missing data, number of subjects with missing data, mean, SD, median, minimum, maximum and CV% will be provided for continuous variables, and counts and percentages for categorical variables.

In each group, all data will be listed by subject, arm, and study day, and summarized by arm and study day. 24-hour urinary BoE, blood COHb, and blood CEVaL biomarker data will be listed and summarized. Absolute and percent change from baseline values will be listed and summarized as appropriate. Descriptive statistics (n, n missing, mean, median, SD, SEM, minimum, maximum, Q1, Q3, CV% and 95%CI) will be used for continuous data variables and frequency counts (n and percentage) for categorical data variables as described in the SAP. Geometric means will also be provided for original biomarker values. Figures will be used to display the data graphically.

Demographics, smoking history, baseline daily cigarette use, mCEQ, spirometry results, Respiratory Symptom Experience Scale, and baseline FTCD scores will be summarized overall and by group, with descriptive statistics for continuous variables and frequency counts and percentage for categorical variables will be provided.

All statistical analyses will be performed with SAS® software version 9.4 or above.

8.1. Determination of Sample Size

A total of 300 subjects will be enrolled in order that 50 subjects for each HTP and Continue Smoking arms will complete the study at the end of confinement phase. There is no target number for per protocol completers for the Smoking Abstinence arm.

This study is being conducted to assess the differences in primary BoE levels after adult smokers switched to Ploom HTP for 5 days.

The sample size estimation is based on the data from a previous study (Haziza et al., 2020). Assuming a Type I error rate of 0.2% for each statistical test of a primary biomarker after multiplicity adjustment using the Bonferroni Method, a two-sided t-test for difference with unequal variances, the sample size of 60 per HTP and Continue Smoking arms enrolled should ensure approximately 50 subjects complete Day 5 assessments and will have 90% power to detect a statistically significant difference in the mean changes of creatinine adjusted values of the primary BoEs (Table 1) between the HTP arm in which adult smoker switched to HTPs for 5 days against the corresponding Continue Smoking arm.

8.2. Analysis Populations

8.2.1. Biomarker of Exposure Population

The BoE population will include subjects from HTP arms who used at least 1 assigned study product, subjects in the Continue Smoking arms, and the subjects in the Smoking Abstinence

arm. To be included in the BoE population, subjects must have baseline (Day -1 to Day 1) and at least 1 post-baseline evaluable BoE data, and must not have any major protocol violations, such as:

- eCO > 8 ppm at two or more consecutive return visits for subjects in the HTP and Smoking Abstinence arms.

8.2.2. Safety Population

The safety population will include all subjects from HTP arms who used at least 1 assigned study product and all subjects from Continue Smoking arms, and all subjects in the Smoking Abstinence arms.

8.2.3. Enrolled Population

The enrolled population will consist of all subjects who signed the informed consent form. This population will include all screen failures.

8.2.4. Product Trial Only Population

The Product Trial Only population includes subjects who participated in the product trial, but who dropped from the study prior to the start of product use on Day 1.

8.2.5. Randomized Population

The Randomized population includes all subjects who are enrolled and randomized according to the randomization schedule.

8.2.6. Subjective Measures Population

The Subjective Measure population includes subjects who used study products and have at least one mCEQ score.

8.2.7. Daily Product Consumption Population

The Daily Product Consumption population includes subjects who are randomized into the HTP arms or Continue Smoking arms and have at least one HTSPD or CPD value.

8.3. Endpoints

8.3.1. Biomarkers

See Section 2.2, Table 2, and Table 3 for the primary and secondary BoEs and BoPH.

8.3.2. Compliance Biomarkers

As per the Schedule of Activities, eCO and the following BoEs will be collected to assess compliance:

- CEMA

- Blood CEVal

CEMA on Day 30 (±3 days) and Day 60 (±3 days) will be assessed via 24-hour urine samples.

8.3.3. Subjective Measures

Modified Cigarette Evaluation Questionnaire, single-item and factor scores.

8.3.4. Daily Product Consumption

- Daily product consumption during the confinement phase (Day 1 to Day 5); ie, CPD and HTSPD per site record.

- Product accountability at return visits during ambulatory phase for HTP arms and self-reported daily product consumption for Continue Smoking arms and Smoking Abstinence arms at return visits during the ambulatory phase (Day 6 to Day 60 [±3 days]).

8.4. Biomarker of Exposure Analyses

8.4.1. Biomarkers of Exposure

A linear mixed models for analysis of covariance will be used to test for statistically significant differences in each primary BoE at Day 5 Day 30 (±3 days), and Day 60 (±3 days) between arms as described in the study objectives, ie, each HTP arm compared to the corresponding Continue Smoking arm, or compared to the Smoking Abstinence arm. In the statistical models, the change from baseline value of a BoE will be included as a dependent variable; arm and gender will be included as fixed effects; and baseline values of corresponding BoE will be included as covariates. The LSM difference, 95% CI for the LSM difference between the Test and Reference, and p-values will be provided. Additional details on BoE analysis will be provided in the SAP.

8.4.2. Biomarkers of Potential Harm and Compliance

Statistical methods for secondary BoEs, BoPHs, and biomarkers of compliance endpoints will be provided in the SAP.

8.5. Subjective Measures

8.5.1. Modified Cigarette Evaluation Questionnaires

Each single mCEQ item will be considered as a 7-point scale and treated as a continuous variable. The responses to the mCEQ will be presented both individually and as the following factor scores based on Cappelleri et al., 2007:

a) Product use satisfaction: average of the response scores from questions 1, 2, and 12;
b) Psychological reward: average of the response scores from questions 4 to 8;
c) Aversion: average of the response scores from questions 9 and 10;

d) Enjoyment of the sensation: response score from question 3;
e) Craving reduction: response score from question 11.

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, median, maximum, Q1, Q3, and 95% CIs) of the factor scores will be provided by gender and overall for each study arm. Individual responses will be listed.

8.6. Exploratory Endpoints

Respiratory Symptom Experience Scales assessments will be performed as indicated in the Schedule of Activities.

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, median, maximum, Q1, Q3, and 95% confidence intervals) of the factor scores will be provided by gender and overall for each study arm. Individual responses to Respiratory Symptom Experience Scales will be listed.

8.6.1. Daily Product Consumption

The number of cigarettes smoked per day and number of HTS used per day during the confinement phrase and the average number of cigarettes smoked per day and average number of HTS used per day during the ambulatory phase will be listed and summarized by study product using descriptive statistics, as appropriate.

8.7. Safety Analysis

The AEs will be coded using the most current version of MedDRA® and summarized by product for the number of subjects reporting the product emergent adverse experience and the number of product emergent adverse experiences reported. An AE listing, including verbatim term, preferred term, study product, severity, and relationship to study product, will be provided. The number of subjects experiencing AEs and the number of AEs will be summarized by study product using frequency counts. Safety data, including laboratory evaluations (as needed), 12-lead ECGs, 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 will be described in the text of the clinical study report. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

All AEs will be listed and summarized using descriptive methodology. Each AE will be coded (to the lowest level term) using MedDRA®. Frequency counts of AEs will be provided by body system, preferred term, and study product. Frequency counts of AEs will also be summarized by severity and relationship to study product.

Observed values for clinical laboratory test data (as needed), 12-lead ECGs, vital signs, and physical examination will be listed.

Spirometry data will be listed and summarized with the appropriate descriptive statistics.

8.8. Interim Analysis

No interim analyses are planned for this study.

9. DATA MANAGEMENT

Data management activities will be detailed in the Data Management Plan (DMP). All data for this study will be captured in the Medrio system, supplied by ALCS or designee. Medrio is 21 Code of Federal Regulations (CFR) Part 11 compliant. Electronic case report forms (eCRF) will be developed according to the study protocol specifications and will follow ALCS data standards. Analytical data will be collected externally to the database.

Data captured on paper source will be entered into the electronic data capture (EDC) system by the site. All data captured will have an audit trail.

Programmed edits 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 are 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.

Adverse experiences will be coded using the most current version of MedDRA®. Concomitant medications will be coded using the most current version of World Health Organization Drug Dictionary. The versions will remain the same throughout the study. Coding will be completed by ALCS Data Management and will be reviewed by the medical monitor at ALCS and the CRO.

All casebooks (eCRFs) will be signed by the Principal Investigator prior to database lock. Submission casebooks will be extracted after database lock and provided to the site.

10. MONITORING OF THE STUDY

The responsible study monitor will contact and visit the Principal Investigator as necessary, and he/she will be allowed, upon request, to inspect and verify all records of the study (eg, source document, ICFs, eCRFs, regulatory documents) in a manner consistent with Good Clinical Practice (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 subject has consented in writing prior to any study procedures being performed. Where the terms of the ICF, GCP, and all other applicable state and federal law permit, the monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Principal 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 internal auditors (or designee), institutional review board (IRB) reviewers, and government inspectors may evaluate the study and must be allowed access to eCRFs, source documents, and other study files.

The Principal Investigator or designee 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. REPORTING FOR THE STUDY

11.1. Case Report Forms

Electronic CRFs will be completed for each screened subject whether or not he/she has completed the study. The Principal Investigator will assure complete and accurate entries on the forms. All eCRFs will be reviewed and signed by the Principal Investigator.

11.2. 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] Quality Assurance (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. ETHICS

12.1. Institutional Review Board/Independent Ethics Committee Approval

12.1.1. 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.

12.1.2. 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, subject 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/IEC and regulatory authority as applicable.

12.2. Written Informed Consent

The nature and purpose of the study will be fully explained to each subject. 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 subject prior to any study procedures being performed. All prospective participants will also sign the VCT consent form and will be checked to verify they are not enrolled in another clinical study prior to the remaining screening procedures.

12.3. Confidentiality

All study sites and vendors will have signed confidentiality agreements with [redacted]. [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 subject 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.

12.4. Ethical Conduct and Responsibility of the Investigator

The Principal 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 Principal 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 Principal 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.

12.5. Procedure for Amendments to the Protocol

No deviations from this protocol will be permitted, except in a medical emergency. The Principal 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.

12.6. Termination of Study

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

12.7. Study Record Retention

Principal Investigator-specific essential documents and all primary data and copies thereof (eg, source documents, eCRFs, laboratory records, data sheets, correspondence, photographs, computer records), 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 Principal 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 (ie, at issuance of final study report), the final data will be transferred to the Sponsor. Subject 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.

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14. APPENDICES

Appendix 1: Adverse Experience Reporting

Definitions

The following is the definition for an **AE**:

Adverse experience means any unfavorable physical or psychological effect in a person that is temporally associated with the use of or exposure to a tobacco product, whether or not the person uses the tobacco product, and whether or not the effect is considered to be related to the use of or exposure to the tobacco product.

All AEs occurring during this study after the subject has signed the ICF and after the first use of the study product during the Product Trial and through Day 60 (±3 days) or EOS/Early Termination 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 product during the Product Trial will be documented as 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.

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

Assessment of Severity

The Principal Investigator (or designee) will review each event and rate each reported sign or symptom on a 3-point severity scale. The following definitions for **rating severity** will be used:

- Mild: The AE is easily tolerated and does not interfere with daily activity
- Moderate: The AE interferes with daily activity, but the subject 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.*

Relationship to Study Product

Each AE will also be assessed by the Principal Investigator (or designee) for **relationship to study product (causality)** using the following grades of certainty (the strength of a causal association may be revised as more information becomes available):

Not related: Clearly and definitely due to extraneous cause (eg, disease, environment)

Unlikely:

a. Does not follow a probable temporal (ie, time) sequence from the 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 subject's clinical state/underlying disease or other drugs or chemicals the subject received.
d. Does not reappear or worsen when the study product is re-administered.

Possible:

a. Follows a reasonable temporal (ie, time) sequence from the use of study product.
b. Follows a known pattern of response to the study product.
c. Could also have been produced by the subject's clinical state/concurrent disease or other drugs or chemicals the subject received.

Likely:

a. Follows a reasonable temporal (ie, time) sequence from the use of study product.
b. Follows a known pattern of response to the study product.
c. Could not readily have been produced by the subject's clinical state/concurrent disease or other drugs or chemicals.
d. Follows a clinically reasonable response on withdrawal (dechallenge), ie, 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 (ie, time) sequence from the use of study product.
b. Follows a known pattern of response to the study product.
c. Cannot be explained by the subject's clinical state/concurrent disease or other drugs or chemicals.
d. Follows a clinically reasonable response on withdrawal (dechallenge), ie, 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 subject is NOT required, but the "definitely related" category may only be used when recurrence is observed.*

Follow-up of Adverse Experiences

Every reasonable effort will be made to follow up with subjects who have ongoing AEs at the EOS visit. Any subject who has an ongoing AE that is possibly related or related to the study product or study procedures at the EOS visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Principal Investigator (or designee) to have stabilized. This will be completed at the Principal Investigator's (or designee's) discretion. Any subject who has an ongoing AE that is not related or unlikely related to the study product or study procedures at the EOS visit can be closed out as ongoing at the Principal Investigator's discretion.

Serious Adverse Experiences

An SAE is defined as any untoward medical occurrence that either:

- Results in death
- Is lifethreatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Principal Investigator at any time after cessation of the study product and considered by the Principal Investigator to be possibly related to the study product, will be reported to the sponsor.

Definition of Life-threatening

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

Adverse experiences requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a clinical assessment form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Experience Reporting

AEs that are associated with the use of the study product and are serious and unexpected will be reported by the study site to the sponsor, medical monitor assigned by the sponsor, and the responsible IRB.

The sponsor and medical monitor will be notified in writing (eg, facsimile, email/attachment) within 24 hours of when a serious, unexpected AE that is associated with use of the study product associated is first recognized or reported.

Subsequently, a written confirmation or summary of the AE (using ALCS SAE Report Form) will be sent to the sponsor within 3 working days of the original notification.

The IRB will be notified of any serious, unexpected AE that is associated with the use of the study product in accordance with the IRB's procedures.

Pregnancy

A positive pregnancy test prior to enrollment will be documented as a screen failure. Pregnancy occurring in a female study subject (after first check-in through EOS/Early Termination) will be documented in a pregnancy form (provided separately) and as a protocol deviation to the IRB.

Pregnancy itself is not an AE. The Principal Investigator or designee will discontinue the pregnant subject from the study and will advise her to seek prenatal care and counseling from her primary care provider. The Principal Investigator (or designee) will refer her to the QuitAssist® 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 subject'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 ALCS Pregnancy Report Form should be completed to report a summary within 3 working days.

The study site staff will request the pregnant subject to notify the site of the outcome of the pregnancy (ie, birth, loss, or termination). To help ensure this, the study site staff will follow up with the subject until the end of pregnancy, if in compliance with the site's standard operating procedures and with the subject's consent. This request and the subject's response will be documented in the subject's source document. A final report of pregnancy outcome will be sent to the medical monitor.

Appendix 2: Clinical Laboratory Evaluations

Serum Chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Chloride Creatinine[c] Glucose Potassium Sodium Total bilirubin[a] Total protein Uric acid	Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination[d] (RBCs, WBCs, casts, and bacteria)
Serology:	**Drug screen:**	**Hormone panel - females only:**
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus (HIV-1 and HIV-2) antibodies	Including but not limited to: Amphetamines/methamphetamines Cocaine (metabolite) Opiates Tetrahydrocannabinol/cannabinoids Alcohol Cotinine test[e]	Follicle-stimulating hormone[f] (postmenopausal females only) Serum pregnancy test[g] (human chorionic gonadotropin) Urine pregnancy test[b]

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.
[b] Performed for all females at check-in. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[c] At screening, estimated glomerular filtration rate will be calculated.
[d] Microscopic examination will be conducted if protein, leukocyte esterase, nitrite, and/or blood are abnormal.
[e] A positive qualitative test (≥ 500 ng/mL) will be required for participation in the study.
[f] To confirm postmenopausal status.
[g] Performed for all females at screening.

Appendix 3: 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 (eg, 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.

Appendix 4: Modified Cigarette Evaluation Questionnaires (mCEQ)

Modified Cigarette Evaluation Questionnaire (mCEQ)

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 - 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?

Appendix 5: Respiratory Symptom Experience Scale

For the following questions, please think about your experiences in the past 30 days and select the appropriate response (Never (0 days out of the last 30 days), Rarely (1-5 days), Occasionally (6-15 days), Most days (16-29 days), Every day (all 30 days out of the last 30 days))

Item 1. Morning Cough

1. Morning cough with phlegm or mucous

Item 2. Cough Frequently

2. Cough frequently throughout the day

Item 3. Shortness of Breath

3. My shortness of breath makes it difficult to do normal daily activities such as walking up a flight of stairs or carrying a heavy object

Item 4. Easily Winded

4. Becoming easily winded during normal daily activities (eg, doing laundry and carrying groceries)

Item 5. Wheezing

5. Wheezing or whistling in your chest at times when you are not exercising or doing other physically strenuous daily activities (eg, while resting)

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