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

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STATISTICAL ANALYSIS PLAN

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Study Product: Ploom Heated Tobacco Product

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Date: 26 March 2024

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

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Issue Date: 26 March 2024

As the statistical analysis plan was executed using the Veeva platform, please find the e-signature page at the end of the document.

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Signature: DocuSigned by: [redacted] C78FAC5F913745B6B7514D09F8A8CA64 [redacted]

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1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the analysis and presentation of the data from this study. Any changes made from the planned analysis described in the protocol or after finalization of this SAP will be documented in the Clinical Study Report (CSR). The section referred to as "Table, Figure, and Listing Shells" within this SAP describes the Clinical Data Interchange Standards Consortium (CDISC) input in order to provide traceability to the corresponding tables, figures, and listings (TFLs). Analysis data model (ADaM) is the source for tables and figures (as well as listings that may contain derived data) and study data tabulation model (SDTM) is the source for the data listings.

Any additional exploratory analyses not addressed within this SAP and/or driven by the data, or requested by Altria Client Services LLC, will be considered out of scope and must be described in the CSR.

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 biomarkers of exposure (BoEs) between heated tobacco product (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 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.

- 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.
- To compare the change in urinary S-benzyl mercapturic acid (S-BMA) levels from baseline, to Day 5 (following 5 days of *ad libitum* use in a confinement setting), Day 30 (±3 days) 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.

2.2 Endpoints

2.2.1 Primary Endpoints

The primary BoEs are presented in Table 2.1.

Table 2.1: 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)
Carboxyhemoglobin	COHb	Carbon monoxide	Blood

2.2.2 Secondary Endpoints

- The secondary BoEs are presented in Table 2.2

Table 2.2: 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)

- Subjective assessments (Modified Cigarette Effects Questionnaire [mCEQ]) among subjects in both HTP and Continue Smoking arms during confinement and ambulatory phases.

- The BoPH are presented in Table 2.3.

Table 2.3: 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)

- Daily product consumption from Day 1 to Day 5 (ie, number of cigarettes smoked per day and number of heated tobacco stick (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 laboratories as needed, and spirometry.

2.2.3 Exploratory Endpoints

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

- Urinary S-BMA levels measured at baseline, Day 5 (following 5 days of ad libitum use in a confinement setting), Day 30 (±3 days) and Day 60 (±3 days; following 55 days of ad libitum use in an ambulatory setting).

3. STUDY DESIGN

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.

- 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.

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

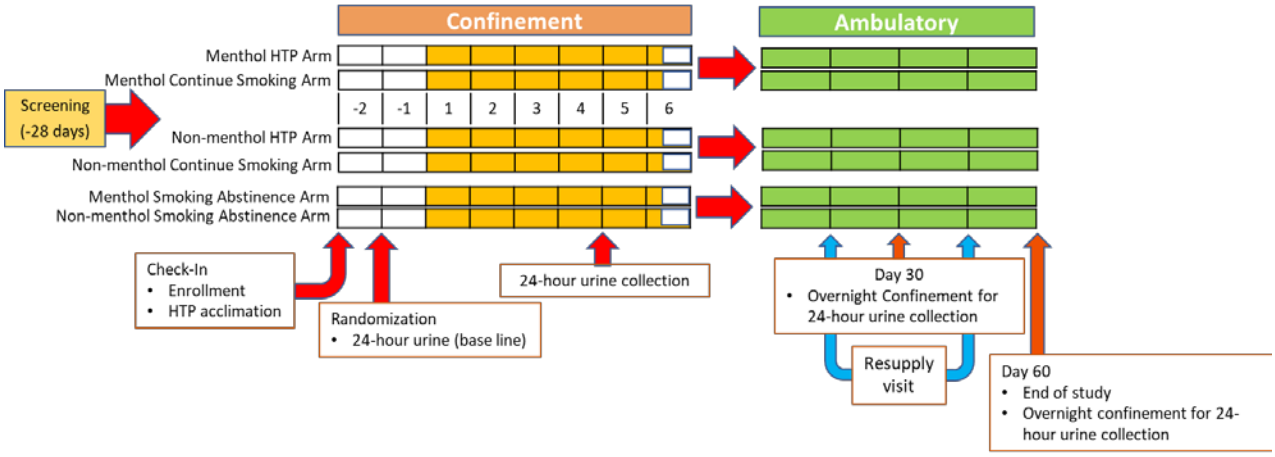
- For Menthol Group:
    - Ploom HTP Menthol HTS arm (n = 60): Subjects will exclusively use the assigned product at least 5 times per day *ad libitum* starting on the morning of Day 1 (after completion of baseline urine collection) through Day 60 (±3 days).
    - Continue Smoking arm (n = 60): Subjects 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 number of cigarettes smoked per day (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 (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 3.1.

Figure 3.1: Study Schematic



Abbreviations: HTP = Heated Tobacco Products.

Confinement Phase:

- Day -2: Check-in, enrollment, HTP Product Trial and *ad libitum* use of usual brand combustible cigarettes (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 (ending at end of confinement in the morning of Day 6)

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.

Ploom HTPs are available in Tobacco and Menthol flavors. As HTPs generate substantially less harmful and potentially harmful constituents (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.

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, 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.

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 (Baseline Period)

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 sex and CPD stratification use (Low </= 16, or High > 16). The three arms are: Ploom HTP, continued cigarette smoking (Continue Smoking) their usual brand combustible cigarettes (UBCC), 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 (Menthol UBCC)	60
	Smoking Abstinence	30
Non-menthol	Ploom HTP Tobacco HTS; R8 (120)	60
	Continue Smoking (Non-menthol UBCC)	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 number of 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 around 7 am). 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.

Day 6 - Day 60 (±3 days) (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.

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)

- Urinary S-BMA levels will be measured at baseline, Day 5 (following 5 days of ad libitum use in a confinement setting), Day 30 (±3 days) and Day 60 (±3 days; following 55 days of ad libitum use in an ambulatory setting).

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

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 urinary CEMA and potentially blood N-(2-cyanoethyl) valine (CEVal) as applicable.

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.

4. 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 between the HTP arm in which adult smoker switched to HTPs for 5 days against the corresponding Continue Smoking arm. The sponsor may end additional recruitment if 50 or more subjects have been randomized and expected to complete day 5 (confinement phase) for each of the HTP and continued smoking groups.

5. ANALYSIS POPULATIONS

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

5.1 Populations for Biomarker Analysis

Three populations will be used for biomarker analysis, as follows.

5.1.1 Modified Intent-to Treat (MITT) Biomarker Population

The MITT biomarker population will include subjects from HTP arms who used at least 1 assigned study product, the subjects in the Continue Smoking arms, and the subjects in the Smoking Abstinence arms. To be included in the MITT biomarker population, subjects must have baseline (Day -1 to Day 1) and at least 1 post-baseline evaluable biomarker data. Subjects who did not meet the inclusion/exclusion criteria and were randomized in error will be excluded from MITT biomarker population.

5.1.2 Per Protocol (PP) Biomarker Population

The PP biomarker population is a subset of MITT biomarker population which will include subjects from the MITT biomarker population who complete the study and do not have any major protocol violation. For the confinement phase of the study, the PP population will include subjects who complete Day 6. For the ambulatory phase of the study, the PP population will include subjects who complete Day 60.

5.1.3 CEMA-compliant Biomarker Population

The CEMA-compliant biomarker population is a subset of the PP biomarker population, which includes only those subjects whose urine creatinine-adjusted CEMA levels present < 30% increase compared to Day 5 or within the upper distribution (e.g., Mean+2SD) of CEMA levels at Day 5 on Day 30 and Day 60 in their respective arm group. This is only for subjects in the HTP and Smoking Abstinence arms. The CEMA-compliant population for Continue Smoking arms will be the same as PP population.

Note: if the number of subjects in the CEMA-compliant population based on the above criteria is less than 50% of the number of subjects in the MITT population for HTP arms, Day 30 will be removed from the criteria and the population will be based solely on Day 60 compared to Day 5. If the number of subjects in the CEMA-compliant population after the modification is still less than 50% of the number of subjects in the MITT population for HTP arms, only descriptive statistics will be presented for CEMA-compliant population without inferential analysis.

Incomplete subject data will be reviewed for validity and included if deemed valid.

5.2 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.

5.3 Enrolled Population

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

5.4 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.

5.5 Randomized Population

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

5.6 Subjective Measures Population

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

5.7 Product Use Population

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

6. PRODUCT DESCRIPTIONS

Study products will be supplied by the sponsor (or designee), along with the batch/lot numbers and certificates of analysis.

Details on study products are listed in Table 6.1.

Table 6.1: 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 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.

The study products to be used in this study are listed below:

Group	Arm	Short Description	Long Description
Menthol	1	Menthol HTS	Ploom HTP Menthol Heated Tobacco Stick; MX3 (681)
	2	Continue Smoking Menthol Cigarette	Continue Smoking of Menthol Usual Brand Combustible Cigarette
	3	Smoking Abstinence (Menthol)	Smoking Abstinence (Menthol)
Non-menthol	4	Tobacco HTS	Ploom HTP Tobacco Heated Tobacco Stick; R8 (120)
	5	Continue Smoking Non-Menthol Cigarette	Continue Smoking of Non-menthol Usual Brand Combustible Cigarette
	6	Smoking Abstinence (Non-Menthol)	Smoking Abstinence (Non-Menthol)

7. BIOMARKER ASSESSMENT AND ANALYSIS

The primary and secondary BoEs and BoPH are listed in Table 2.1, Table 2.2 and Table 2.3.

7.1 Biomarkers Sample Collection

Urine Biomarker (BoE, BoPH) Collection

A 24-hour urine collection will be performed at the following scheduled timepoints.

Baseline and Day 5: 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).

Day 30 and Day 60: 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).

Blood Biomarker (BoE, BoPH) Collection

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.

7.2 Bioanalytical Method

Urine aliquots for urine biomarkers of exposure and potential harm and blood samples for sICAM-1 will be shipped to [redacted] Bioanalytical Services for analysis. These samples, with the exception of sICAM-1, COHb and Hemoglobin, will be analyzed using validated LC-MS/MS analytical methods. sICAM-1 and hemoglobin will be measured by validated ligand binding assays. The samples for COHb will be determined using a validated spectrophotometric method. The samples for future evaluation will be stored indefinitely and may be used to measure various biomarkers associated with tobacco use.

Blood samples for CEVal analysis will be shipped to the [redacted] Bioanalytical Services for analysis. Whole blood samples will be processed into rinsed erythrocytes and then frozen to lyse the cells. The CEVal evaluation will be determined by a measurement of both cyanoethylvaline adducts in rinsed erythrocytes with a validated LC-MS/MS method. The same rinsed erythrocyte samples will be used to measure the total hemoglobin in the sample with a validated ligand binding method. Blood samples for WBC count and serum samples for HDL concentration analysis will be shipped to LabConnect (Johnson City, TN) for analysis.

The lower limit of quantification (LLOQ) values for urine and blood biomarkers of exposure and potential harm are shown in the table below.

Analyte	LLOQ
<u>TNeq:</u>	
Nicotine	50.0 ng/mL
Cotinine	50.0 ng/mL
3HC	50.0 ng/mL
Nicotine glucuronide	50.0 ng/mL
Cotinine glucuronide	200 ng/mL
3HC glucuronide	200 ng/mL
NNN	0.200 pg/mL
NNAL	5.00 pg/mL
4-ABP	1.00 pg/mL
3-OH BaP	25.0 fg/mL
CEMA	0.275 ng/mL

3-HPMA	20.0 ng/mL
HMPMA	20.0 ng/mL
MHBMA	0.100 ng/mL
S-PMA	25.0 pg/mL
S-BMA	100 pg/mL
HEMA	0.100 ng/mL
1-AN	2.00 pg/mL
2-AN	2.00 pg/mL
11-DTX-B2	25.0 pg/mL
8-epi $PGF_{2\alpha}$	25.0 pg/mL
sICAM-1	12.5 ng/mL
COHb	0.2%
CEVal	3.00 pmol/g
Creatinine	50.0 µg/mL
Hemoglobin	2.00 mg/mL

Note: 3HC = trans-3'-hydroxycotinine

7.3 Urine Biomarker Analysis Variables

The following urine biomarker variables will be determined:

- Measured concentration
- Total biomarker mass excreted per 24 hours
- Absolute change from baseline in total biomarker mass excreted per 24 hours
- Percent change from baseline in total biomarker mass excreted per 24 hours

Urine biomarker 24-hour amount excreted will be calculated as shown in Section 7.3.1. Absolute and percent change from baseline will be calculated as shown in Section 7.3.2.

In addition, creatinine-adjusted concentrations will be calculated for urine biomarkers, as shown in Section 7.3.3.

7.3.1 Urine Biomarker 24-hour Amount excreted

Urine Nicotine Equivalents

Nicotine equivalents (TNeq) will be calculated as the molar sum of nicotine and 5 major nicotine metabolites excreted in urine over 24 hours. Values of individual components

reported as below the limit of quantitation (BLQ) will be set to one-half of the lower limit of quantitation (LLOQ) prior to use in the calculation below. Missing urine data will not be imputed.

The concentration of nicotine and each metabolite will first be multiplied by the 24-hour urine volume to obtain the total amount excreted in 24 hours, then divided by the molecular weight of the metabolite to obtain the total amount of each in moles. The sum in moles will then be converted to mass of TNeq by multiplying by the molecular weight of nicotine.

Nicotine (mg/24h)	=	nicotine concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Nicotine-glucuronide (mg/24h)	=	nicotine glucuronide concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Cotinine (mg/24 hours)	=	cotinine concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Cotinine-glucuronide (mg/24h)	=	cotinine glucuronide concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
3HC (mg/24h)	=	trans-3'-hydroxycotinine concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
3HC-glucuronide (mg/24h)	=	trans-3'-hydroxycotinine glucuronide concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
TNeq (mg/24 hours)	=	(nicotine [mg/24h]/162.23 [mg/mmol] + nicotine-gluc [mg/24h]/338.36 [mg/mmol] + cotinine [mg/24h]/176.22 [mg/mmol] + cotinine-gluc [mg/24h]/352.34 [mg/mmol] + 3HC [mg/24h]/192.22 [mg/mmol] + 3HC-gluc [mg/24h]/368.34 [mg/mmol]) x 162.23 (mg/mmol)

Other Urine biomarkers

Amount of urine biomarker excreted in urine over 24 hours will be calculated based on the urine biomarker concentration and urine volume. Values reported as BLQ will be set to one-half of the LLOQ prior to use in the calculations below. Missing urine data will not be imputed.

Urine biomarker (unit2) = Urine biomarker concentration (unit1) x urine volume (mL/24 hours)/1000

Note: if unit1 is reported as pg/mL, unit2 will be ng/24 hours. If unit1 is reported as ng/mL, unit2 will be µg/24 hours.

7.3.2 Urine Biomarker Change From Baseline

Urine biomarker change from baseline will be calculated for the 24-hour amount excreted values of urine biomarkers of exposure and potential harm as follows:

Absolute change from baseline = Post Product Use Value – Baseline Value

Percent change from baseline (%) = [(Post Product Use Value – Baseline Value) / Baseline Value] x 100%

7.3.3 Creatinine Adjustments of Urine Biomarker Concentrations

Creatinine-adjusted NE concentration will be reported in µg/mL as follows:

TNeq concentration (µg/mL) = (nicotine [ng/mL]/162.23 [mg/mmol] + nicotine-gluc [ng/mL]/338.36 [mg/mmol] + cotinine [ng/mL]/176.22 [mg/mmol] + cotinine-gluc [ng/mL]/352.34 [mg/mmol] + 3HC [ng/mL]/192.22 [mg/mmol] + 3HC-gluc [ng/mL]/368.34 [mg/mmol]) × 162.23 (mg/mmol) × 1 µg/1000 ng

Then the TNeq will be adjusted as follows:

$$\text{Adjusted Nicotine equivalents (mg /g creatinine)} = \frac{\text{TNeq concentration (µg/mL)} \times 100}{\text{Creatinine concentration (mg/dL)}}$$

For other biomarkers:

$$\text{Adjusted Urine biomarker (unit2/g creatinine)} = \frac{\text{Urine biomarker concentration (unit1/mL)} \times 100}{\text{Creatinine concentration (mg/dL)}}$$

Where: if unit1 = pg, then unit2 = ng, and if unit1 = ng, then unit2 = µg.

For creatinine values that are BLQ, the values will not be used to adjust the urine biomarker concentration values. The creatinine-adjusted urinary biomarker values will be treated as missing.

Creatinine-adjusted values, absolute change from baseline, and percent change from baseline will be presented.

7.4 Blood Biomarker Analysis Variables

The following variables will be determined for blood biomarkers:

- Blood COHb saturation, sICAM-1 concentration, WBC count, HDL and CEVal concentration (measured values)
- Absolute change from baseline (calculated for each biomarker based on individual measured values)
- Percent change from baseline (calculated for each biomarker based on individual measured values)

Absolute and percent change from baseline will be calculated as shown in Section 7.3.2. Values that are BLQ for sICAM-1 and COHb saturation will be treated as one-half the LLOQ. Baseline for blood biomarkers is the Visit 1 value.

7.5 Data Summarization and Presentation

The descriptive statistics tables for blood, urine, and exhaled breath biomarkers will be generated with the following level of precision for the summary statistics:

- Number of observations (n) without a decimal;
- Minimum/maximum in same precision as in the database
- Arithmetic mean (mean), geometric mean (Geo. mean), and median with one more decimal/significant figure than minimum/maximum;
- Q1 and Q3 with one more decimal/significant figure than minimum/maximum;
- Standard deviation (SD)/standard error of the mean (SEM) with one more decimal/significant figure than mean/median.
- Coefficient of variance (CV%) with one decimal;

The derived values (amount excreted in urine biomarkers and percent change from baseline) will have two decimal places. Change from baseline will have the same precision as the original values (2 decimal places for urine biomarkers and same precision as reported concentrations for blood and exhaled breath biomarkers).

Figures for mean biomarker and absolute and percent change from baseline versus visit by arm and boxplots of biomarker and absolute change from baseline by arm and visit will be presented for each biomarker.

7.5.1 Urine Biomarkers

Urine biomarker analysis variables (including concentrations for each component of TNeq) will be listed by arm, subject, and study visit. All BLQ values will be presented as “BLQ” in the listings.

The total mass excreted per 24 hours and absolute and percent change from baseline in total mass excreted per 24 hours will be summarized by arm, sex, and visit for each urine biomarker using the following descriptive statistics: n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum. The descriptive statistics will be provided for the BoE population.

In addition, creatinine-adjusted concentrations, absolute change from baseline in creatinine-adjusted concentrations, and percent change from baseline in creatinine-adjusted concentrations will also be summarized.

7.5.2 Blood Biomarkers

Blood biomarker analysis variables will be listed by arm, subject, and study visit. Values that are BLQ will be presented as "BLQ" in the listings.

Blood biomarker concentration, absolute change from baseline, and percent change from baseline will be summarized by arm, sex, and visit using the same descriptive statistics as the urine biomarker data. Blood biomarker concentration values that are BLQ will be treated as one-half of the LLOQ. The descriptive statistics will be provided for the BoE population.

7.6 Statistical Analyses

7.6.1 Hypothesis and Study Product Comparisons

The hypothesis for the study is 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.

The hypothesis to be tested for the primary BoEs is:

BoEs are significantly reduced in each HTP arm (Arms 1 and 4) compared to the continue to smoke arm (Arm 2 and 5).

$$H_0: \mu_{HTP} \leq \mu_{CC} \text{ vs. } H_1: \mu_{HTP} > \mu_{CC}$$

Where μ_{HTP} is the change from baseline for respective HTP arms and μ_{CC} is the change from baseline for the continue to smoke arm, between baseline (Day -1) and post-product switch (Day 5) for primary BoE.

7.6.2 Primary Endpoint Analysis

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. As Day 5 is under confinement

phase and Days 30 and 60 are under ambulatory phase, the statistical analysis will be performed for Day 5 and Days 30 and 60 separately.

For Day 5, in the statistical models, the change from baseline value of a BoE (creatinine-adjusted for urine BoE) will be included as a dependent variable; arm, sex, and CPD strata will be included as fixed effects; and age and baseline values of corresponding BoE (creatinine-adjusted for urine BoE) will be included as covariates. Study site will be used as a random effect. The least-squares means (LSM) difference, 95% CI for the LSM difference between the Test and Reference, and p-values will be provided.

The analysis will be conducted on the MITT, PP, and CEMA-compliant biomarker populations. The analysis will be performed for each study group (Menthol and Non-menthol) separately.

The following SAS codes will be used to perform the analysis.

```
Proc mixed data=< >;
By group;
Class site sex arm CPD;
Model response = sex arm CPD age baseline /ddfm=kr;
Random site;
Estimate “HTP vs Continue Smoking” Arm 1 -1 0/CL alpha=0.05;
Estimate “HTP vs Smoking Abstinence” Arm 1 0 -1/CL alpha=0.05;
LSmeans arm;
Run;
```

Programmer note: if sex is statistically significant, an estimate statement for sex effect will be added into the SAS codes and the results will be included in the SAS outputs.

The primary endpoint comparisons are as follow:

Menthol group:

Arm 1 versus Arm 2 at Day 5
Arm 1 versus Arm 3 at Day 5

Non-menthol group:

Arm 4 versus Arm 5 at Day 5
Arm 4 versus Arm 6 at Day 5

For Days 30 and 60, in the statistical models, the change from baseline value of a BoE (creatinine-adjusted for urine BoE) will be included as a dependent variable; arm, sex, visit, and CPD strata, and arm by visit interaction will be included as fixed effects; site as a random effect, and age and baseline values of corresponding BoE (creatinine-adjusted for

urine BoE) will be included as covariates. Study site will be used as a random effect. Visit will be treated as a repeated measurement and Unstructure (UN) will be used as variance-covariance structure. The least-squares means (LSM) difference, 95% CI for the LSM difference between the Test and Reference, and p-values will be provided.

The analysis will be conducted on the MITT, PP, and CEMA-compliant population. The analysis will be performed for each study group (Menthol and Non-menthol) separately.

The following SAS codes will be used to perform the analysis.

Proc mixed data=< >;
By group;
Class subject site sex arm visit CPD;
Model response = sex arm CPD age visit arm*visit baseline /ddfm=kr;
Random site;
Repeated visit/type=UN subject=subject;
Estimate “HTP vs Continue Smoking at Day 30” Arm 1 -1 0 Arm*Visit 1 0 -1 0 0 0/CL alpha=0.05;
Estimate “HTP vs Smoking Abstinence at Day 30” Arm 1 0 -1 Arm*Visit 1 0 0 0 -1 0/CL alpha=0.05;
Estimate “HTP vs Continue Smoking at Day 60” Arm 1 -1 0 Arm*Visit 0 1 0 -1 0 0/CL alpha=0.05;
Estimate “HTP vs Smoking Abstinence at Day 60” Arm 1 0 -1 Arm*Visit 0 1 0 0 0 -1/CL alpha=0.05;
LSmeans arm arm*visit;
Run;

Programmer note: if sex is statistically significant, an estimate statement for sex effect will be added into the SAS codes and the results will be included in the SAS outputs.

The primary endpoint comparisons are as follow:

Menthol group:

Arm 1 versus Arm 2 at Day 30
Arm 1 versus Arm 3 at Day 30
Arm 1 versus Arm 2 at Day 60
Arm 1 versus Arm 3 at Day 60

Non-menthol group:

Arm 4 versus Arm 5 at Day 30
Arm 4 versus Arm 6 at Day 30
Arm 4 versus Arm 5 at Day 60
Arm 4 versus Arm 6 at Day 60

The analysis will be focused on the comparisons listed above. The comparisons to nonsmoking group is not part of the hypothesis but is more for informational purposes.

Given the sample size of the study and linear mixed model is very robust, the analysis will be performed based on the original scale without data transformation.

7.6.3 Secondary Endpoint Analysis

The same statistical analysis model defined in the primary analysis Section 7.6.2 will also be used for secondary endpoint (BoE and BoPH) analysis.

7.6.4 Exploratory Analysis

An exploratory analysis will be performed on the BoPH biomarkers. In this analysis, the HTP (Menthol) and HTP (Non-menthol) groups will be combined as the Ploom HTP (Combined) group; the continue smoking of menthol and non-menthol UBCC groups will be combined as Continue Smoking (Combined) group; and the Smoking Abstinence (Menthol) and Smoking Abstinence (Non-menthol) groups will be combined as Smoking Abstinence (Combined) group. Descriptive statistics will be reported for the above three combined groups by timepoint. The same statistical analysis model defined in the primary analysis Section 7.6.2, with flavor (Menthol, Non-menthol) and group by flavor interaction as a fixed effects added to the model will also be used for this exploratory analysis. The summarization and statistical analysis will be performed on the MITT, PP and CEMA-Compliant populations.

7.7 Subjective Measures

7.7.1 Modified Cigarette Evaluation Questionnaires

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 that subject checks in for overnight confinements for Day 30 (+/- 3 days) and Day 60 (+/- 3 days).

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 and questions as defined in the protocol based on Cappelleri et al:

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 sex and overall for each study arm. Individual responses will be listed.

7.8 Product Use

The number of CPD and number of HTS used per day during the confinement phase 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 and sex using descriptive statistics. For Day 15/30/45/60, Subject reported CPD, subject reported HTS per day and calculated HTSs per day based on the difference between dispensed and returned number of HTSs will be used for the summarization. For the intervals between visits, the average number of HTS product use per day will be calculated using the difference between number dispensed and number returned divided by the number of days between visits.

7.9 Exploratory Endpoints

Respiratory Symptom Experience Scale (RSES) assessments (Shiffman *et. al.*, 2023) will be performed on Day -1, Day 30 (+/- 3 days), and Day 60 (+/- 3 days). During an ambulatory phase of the study, the Respiratory Symptom Experience Scale assessments should be performed at check-in on Day 29 (± 3 days) for the Day 30 confinement visit, and at check-in on Day 59 (± 3 days) for the Day 60 confinement visit.

The RSES will be assessed with 5 items:

For the following questions, please think about your experiences in the past 30 days:

1. Morning cough with phlegm or mucus
2. Cough frequently throughout the day
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
4. Becoming easily winded during normal daily activities (e.g., doing laundry and carrying groceries)
5. Wheezing or whistling in your chest at times when you are not exercising or doing other physically strenuous daily activities (e.g., while resting)

The response options for each RSES assessment item will be:

- 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)

The score for each RSES assessment item will be 1 through 5 ranging from 1 = Never (0 days out of the last 30 days) to 5 = Every day (all 30 days out of the last 30 days). A

composite score will be calculated by taking the average of the 5 RSES items. If an item is missing, a composite will not be calculated.

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, median, maximum, Q1, Q3, and 95% confidence intervals) of composite score and change from baseline in composite score will be provided by sex and overall for each study arm. Individual responses to Respiratory Symptom Experience Scale will be listed.

In each group, linear mixed models for analysis of covariance (ANCOVA) will be used to compare the Day 30 (±3 days), and Day 60 (±3 days) RSES composite score between arms, i.e., each HTP arm compared to the corresponding Continue Smoking arm, or compared to the Smoking Abstinence arm. The same statistical model used in the biomarker analysis for Day 30 and Day 60 will be used for the analysis.

7.10 Preliminary Data and Interim Analysis

[redacted] Biometrics will not perform preliminary or interim analyses.

8. SAFETY

All relevant electronic case report form (eCRF) and clinical laboratory data will be listed by subject and chronologically by assessment time point. This will include rechecks, unscheduled, and early termination assessments.

Applicable continuous variables will be summarized using n, mean, SD, minimum, median, and maximum.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Percentages will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

Baseline will be the result closest and prior to the first product administrated on Day 1 unless otherwise stated. Summaries for post-baseline time points will not include rechecks, unscheduled, or early termination (ET) measurements.

Tables summarizing safety data by assessment time point will only include summaries for baseline and post-baseline time points by arm, group, and overall.

8.1 Subject Disposition

Subjects will be summarized by number of subjects enrolled, randomized/assigned arm, not randomized and reason, completed, and discontinued the study product use and discontinued from the study with discontinuation reasons by arm within group and overall. Summarization will be performed on the safety and BoE populations.

8.2 Protocol Deviations

Protocol Deviations will be entered into the electronic data capture (EDC) system by the sites. There are also edit checks that are marked as 'Protocol Deviations' that will be reviewed by Data Management and the study team, as applicable, to ensure all required deviations are entered.

The Protocol Deviations will be reviewed on an ongoing basis. If a protocol deviation is identified during a site visit, the clinical research associate (CRA) can issue a query to have the deviation entered into the Medrio system. This same process can be followed by data management.

The 'Important, Not Important' category will be entered by the site based on the protocol deviation definition document. This information will be reviewed by Altria during listing reviews prior to database freeze. Sites will be queried if the 'Important, Not Important' category needs to be modified.

Protocol deviations will be listed.

8.3 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) by randomized/assigned arm, group, and overall. Age that was collected on the CRF at screening will be used for analysis.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) for each randomized/assigned arm, group, and overall.

Summarization will be performed on the safety and BoE populations.

8.4 Smoking History

Usual brand attributes, tobacco and nicotine product use, and Fagerström test for cigarette dependence (FTCD) will be assessed at screening.

Descriptive statistics will be calculated for continuous variables (average cigarettes smoked per day [CPD], number of years smoked, and FTCD score) by randomized arm, group, and overall. Total FTCD score will be calculated based on the responses for the six questions in the questionnaire and used as the analysis variable for FTCD. The total score will be recorded directly in the database.

Frequency counts will be provided for categorical variables (subject's usual brand, and flavor) for each randomized arm, group, and overall.

Summarization will be performed on the safety and BoE populations.

8.5 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 26.0.

A PUEAE is defined as an AE that is starting or worsening at the time of or after the first randomized study product use. Each PUEAE will be attributed to the product or arm based on the onset date and time of the AE.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, arm, severity, relationship to study product, and action; however, only product use-emergent AEs (PUEAEs) will be summarized. For the arms which subjects did not use the study products (Arms 3 and 6), the PUEAE will be counted after the subjects completed the baseline assessments (the same timeframe as the subjects in Arms 1, 2, 4, and 5).

If the onset time of an AE is missing and the onset date is the same as the first study product use date, then the AE will be considered product use emergent in the study product. If onset time of an AE is missing and the onset date does not fall on a study product use date, then the AE will be considered product use emergent for the study product administered. If the onset date of an AE is missing, then the AE will be considered product use emergent, unless the onset date is known to have occurred prior to the first study product use.

PUEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the PUEAE and as percent of number of subjects who used study product by arm and overall. The number of PUEAEs will be tabulated in a similar manner. A table which summarizes the number of PUEAEs by severity and relationship to study product will also be included.

In addition, AEs that occurred during product trial and baseline periods will be summarized separately.

Serious adverse events (SAEs), if present, will also be listed. Applicable narratives will be included in the CSR.

8.6 Clinical Laboratory Tests (Chemistry, Hematology, and Urinalysis)

Serum chemistry, hematology, and urinalysis samples will be collected at screening and listed by subject. Reference ranges will be listed.

Clinical laboratory results will be presented in standard international (SI) units. Out-of-reference range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results.

Out-of-reference range values and corresponding recheck results will be listed.

8.7 Vital Signs

Vital signs (heart rate, blood pressure, temperature, and respiratory rate) will be measured at Screening, Day -2, Day 6, and End of Study (Day 60) or early termination.

Descriptive statistics will be reported for vital sign measurements by arm and visit. Baseline is the last non-missing value including recheck and unscheduled event before randomization/assignment.

8.8 Electrocardiogram

A single 12-lead ECG will be recorded at Screening and will be listed by subject.

8.9 Prior and Concomitant Medications

Prior and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Drug Dictionary Version 01MAR2023 B3 and listed.

8.10 Physical Examination

Physical examination is required at screening and as part of the end of study (EOS)/ ET assessment. Symptom-driven physical examinations are not required for each day of confinement; as the name suggests, it will only occur if and when the subject complains of new physical symptom/s during the study that was not present during the initial physical examination or to investigate adverse experience at Principal Investigator’s discretion. Physical examinations will be listed by subject.

8.11 Lung Function (Spirometry)

A spirometry assessment, both pre- and post-administration of a short-acting bronchodilator, will be performed at Screening. Spirometry without administration of a bronchodilator will be performed at Day 60 (±3 days) or in case of ET from the study. Spirometry predicted values will be standardized to the Global Lungs Initiative predictive set.

Spirometry will be used to measure peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory flow (FEF 25-75%), and forced expiratory volume in 1 second (FEV1) as well as the percent predicted values.

Descriptive statistics will be reported for measured and percent of predicted spirometry parameters and change from baseline by arm and visit. Baseline is the last non-missing value including recheck and unscheduled event before randomization/assignment for pre-bronchodilator measurement. Results prior to baseline will only be listed. At the end of study, only pre-bronchodilator measurement and change from baseline will be summarized.

Spirometry results will be listed by subject.

9. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol except the following item:

- The protocol did not include site as a factor in the statistical model. As this is a multi-center study, site was added as a random effect in the statistical model for biomarker analysis.

10. SUMMARY TABLES, FIGURES, AND LISTINGS

Summary tables and figures are numbered following the International Council on Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all summary tables and figures will be generated using SAS® Version 9.4 or higher.

10.1 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

Number	Title	Shell
Table 14.1.1	Summary of Disposition (Enrolled/Product Trial/Randomized/Safety/MITT/PP/CEMA Compliant Populations)	CDS
Table 14.1.2	Demographic Summary (Safety/ MITT/PP/CEMA Compliant Populations)	CDEM
Table 14.1.3	Tobacco and Nicotine Product Use Summary (Safety/ MITT/PP/CEMA Compliant Populations)	CTNH

Number	Title	Shell
Table 14.1.4	Usual Brand Summary (Safety/ MITT/PP/CEMA Compliant Population)	CUB
Table 14.1.5	FTCD Score Summary (Safety/ MITT/PP/CEMA Compliant Populations)	CFT

14.2 Biomarker and Study Product Use Data Summary Tables and Figures

14.2.1 Biomarker Tables

14.2.1.1 Urine NNAL Tables

Number	Title	Shell
Table 14.2.1.1.1	Summary of Urine NNAL Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.1.2	Summary of Urine NNAL Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.1.3	Summary of Urine NNAL Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.1.4	Summary of Urine NNAL Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.1.5	Summary of Urine NNAL Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.1.6	Summary of Urine NNAL Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.1.7	Statistical Comparisons of Urine NNAL Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.1.8	Statistical Comparisons of Urine NNAL Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.1.9 through Table 14.2.1.1.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.1.17 through Table 14.2.1.1.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.2 Urine NNN Tables

Number	Title	Shell
Table 14.2.1.2.1	Summary of Urine NNN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.2.2	Summary of Urine NNN Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.2.3	Summary of Urine NNN Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.2.4	Summary of Urine NNN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.2.5	Summary of Urine NNN Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.2.6	Summary of Urine NNN Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.2.7	Statistical Comparisons of Urine NNN Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.2.8	Statistical Comparisons of Urine NNN Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat1

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.2.9 through Table 14.2.1.2.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.2.17 through Table 14.2.1.2.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.3 Urine 2-MHBMA Tables

Number	Title	Shell
Table 14.2.1.3.1	Summary of Urine 2-MHBMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.3.2	Summary of Urine 2-MHBMA Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.3.3	Summary of Urine 2-MHBMA Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.3.4	Summary of Urine 2-MHBMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.3.5	Summary of Urine 2-MHBMA Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.3.6	Summary of Urine 2-MHBMA Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.3.7	Statistical Comparisons of Urine 2-MHBMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.3.8	Statistical Comparisons of Urine 2-MHBMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.3.9 through Table 14.2.1.3.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.3.17 through Table 14.2.1.3.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.4 Urine 3-HPMA Tables

Number	Title	Shell
Table 14.2.1.4.1	Summary of Urine 3-HPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.4.2	Summary of Urine 3-HPMA Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.4.3	Summary of Urine 3-HPMA Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.4.4	Summary of Urine 3-HPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.4.5	Summary of Urine 3-HPMA Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.4.6	Summary of Urine 3-HPMA Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.4.7	Statistical Comparisons of Urine 3-HPMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.4.8	Statistical Comparisons of Urine 3-HPMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.4.9 through Table 14.2.1.4.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.4.17 through Table 14.2.1.4.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.5 Urine SPMA Tables

Number	Title	Shell
Table 14.2.1.5.1	Summary of Urine SPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1

Table 14.2.1.5.2	Summary of Urine SPMA Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.5.3	Summary of Urine SPMA Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.5.4	Summary of Urine SPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.5.5	Summary of Urine SPMA Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.5.6	Summary of Urine SPMA Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.5.7	Statistical Comparisons of Urine SPMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.5.8	Statistical Comparisons of Urine SPMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.5.9 through Table 14.2.1.5.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.5.17 through Table 14.2.1.5.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.6 Urine HEMA Tables

Number	Title	Shell
Table 14.2.1.6.1	Summary of Urine HEMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.6.2	Summary of Urine HEMA Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1

Table 14.2.1.6.3	Summary of Urine HEMA Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.6.4	Summary of Urine HEMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.6.5	Summary of Urine HEMA Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.6.6	Summary of Urine HEMA Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.6.7	Statistical Comparisons of Urine HEMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.6.8	Statistical Comparisons of Urine HEMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.6.9 through Table 14.2.1.6.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.6.17 through Table 14.2.1.6.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.7 Urine 1-AN Tables

Number	Title	Shell
Table 14.2.1.7.1	Summary of Urine 1-AN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.7.2	Summary of Urine 1-AN Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.7.3	Summary of Urine 1-AN Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.7.4	Summary of Urine 1-AN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.7.5	Summary of Urine 1-AN Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.7.6	Summary of Urine 1-AN Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.7.7	Statistical Comparisons of Urine 1-AN Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.7.8	Statistical Comparisons of Urine 1-AN Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.7.9 through Table 14.2.1.7.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.7.17 through Table 14.2.1.7.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.8 Urine 2-AN Tables

Number	Title	Shell
Table 14.2.1.8.1	Summary of Urine 2-AN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.8.2	Summary of Urine 2-AN Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.8.3	Summary of Urine 2-AN Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.8.4	Summary of Urine 2-AN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.8.5	Summary of Urine 2-AN Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.8.6	Summary of Urine 2-AN Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.8.7	Statistical Comparisons of Urine 2-AN Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.8.8	Statistical Comparisons of Urine 2-AN Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.8.9 through Table 14.2.1.8.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.8.17 through Table 14.2.1.8.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.9 Urine CEMA Tables

Number	Title	Shell
Table 14.2.1.9.1	Summary of Urine CEMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.9.2	Summary of Urine CEMA Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.9.3	Summary of Urine CEMA Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.9.4	Summary of Urine CEMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.9.5	Summary of Urine CEMA Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.9.6	Summary of Urine CEMA Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.9.7	Statistical Comparisons of Urine CEMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.9.8	Statistical Comparisons of Urine CEMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.9.9 through Table 14.2.1.9.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.9.17 through Table 14.2.1.9.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.10 Urine 3-OH-B[a]P Tables

Number	Title	Shell
Table 14.2.1.10.1	Summary of Urine 3-OH-B[a]P Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.10.2	Summary of Urine 3-OH-B[a]P Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.10.3	Summary of Urine 3-OH-B[a]P Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.10.4	Summary of Urine 3-OH-B[a]P Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.10.5	Summary of Urine 3-OH-B[a]P Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.10.6	Summary of Urine 3-OH-B[a]P Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.10.7	Statistical Comparisons of Urine 3-OH-B[a]P Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between	CBStat1

Number	Title	Shell
	HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	
Table 14.2.1.10.8	Statistical Comparisons of Urine 3-OH-B[a]P Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.10.9 through Table 14.2.1.10.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.10.17 through Table 14.2.1.10.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.11 Urine HMPMA Tables

Number	Title	Shell
Table 14.2.1.11.1	Summary of Urine HMPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.11.2	Summary of Urine HMPMA Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.11.3	Summary of Urine HMPMA Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.11.4	Summary of Urine HMPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.11.5	Summary of Urine HMPMA Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.11.6	Summary of Urine HMPMA Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.11.7	Statistical Comparisons of Urine HMPMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1

Number	Title	Shell
Table 14.2.1.11.8	Statistical Comparisons of Urine HMPMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.11.9 through Table 14.2.1.11.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.11.17 through Table 14.2.1.11.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.12 Urine 4-ABP Tables

Number	Title	Shell
Table 14.2.1.12.1	Summary of Urine 4-ABP Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.12.2	Summary of Urine 4-ABP Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.12.3	Summary of Urine 4-ABP Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.12.4	Summary of Urine 4-ABP Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.12.5	Summary of Urine 4-ABP Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.12.6	Summary of Urine 4-ABP Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.12.7	Statistical Comparisons of Urine 4-ABP Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1

Number	Title	Shell
Table 14.2.1.12.8	Statistical Comparisons of Urine 4-ABP Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.12.9 through Table 14.2.1.12.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.12.17 through Table 14.2.1.12.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.13 Urine SBMA Tables

Number	Title	Shell
Table 14.2.1.13.1	Summary of Urine SBMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.13.2	Summary of Urine SBMA Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.13.3	Summary of Urine SBMA Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.13.4	Summary of Urine SBMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.13.5	Summary of Urine SBMA Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.13.6	Summary of Urine SBMA Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.13.7	Statistical Comparisons of Urine SBMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1

Number	Title	Shell
Table 14.2.1.13.8	Statistical Comparisons of Urine SBMA Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.13.9 through Table 14.2.1.13.16) and for the CEMA-compliant Biomarker Population (Table 14.2.1.13.17 through Table 14.2.1.13.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.14 Blood COHb Tables

Number	Title	Shell
Table 14.2.1.14.1	Summary of Blood COHb (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.14.2	Summary of Blood COHb (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.14.3	Summary of Blood COHb Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.14.4	Statistical Comparisons of Blood COHb (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.14.5	Statistical Comparisons of Blood COHb (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.14.6 through Table 14.2.1.14.10) and for the CEMA-compliant Biomarker Population (Table 14.2.1.14.11 through Table 14.2.1.14.14). No Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.15 Urine NE Tables

Number	Title	Shell
Table 14.2.1.15.1	Summary of Urine NE Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.15.2	Summary of Urine NE Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.15.3	Summary of Urine NE Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.15.4	Summary of Urine NE Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.15.5	Summary of Urine NE Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.15.6	Summary of Urine NE Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.15.7	Statistical Comparisons of Urine NE Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.15.8	Statistical Comparisons of Urine NE Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.15.9 through Table 14.2.1.15.16) and for the CEMA-compliant biomarker Population (Table 14.2.1.15.17 through Table 14.2.1.15.23). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.16 Blood CEVal Tables

Number	Title	Shell
Table 14.2.1.16.1	Summary of Blood CEVal (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.16.2	Summary of Blood CEVal (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.16.3	Summary of Blood CEVal Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.16.4	Statistical Comparisons of Blood CEVal (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.16.5	Statistical Comparisons of Blood CEVal (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.16.6 through Table 14.2.1.16.10) and for the CEMA-compliant Biomarker Population (Table 14.2.1.16.11 through Table 14.2.1.16.14). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.17 Blood sICAM-1 Tables

Number	Title	Shell
Table 14.2.1.17.1	Summary of Blood sICAM-1 (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.17.2	Summary of Blood sICAM-1 (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.17.3	Summary of Blood sICAM-1 Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.17.4	Statistical Comparisons of Blood sICAM-1 (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.17.5	Statistical Comparisons of Blood sICAM-1 (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.17.6 through Table 14.2.1.17.10), for the CEMA-compliant Biomarker Population (Table 14.2.1.17.11 through Table 14.2.1.17.14), for the MITT Biomarker Population (Combined) (Table 14.2.1.17.15 through Table 14.2.1.17.19), for the PP Biomarker Population (Combined) (Table 14.2.1.17.20 through Table 14.2.1.17.24), and for the CEMA-compliant Biomarker Population (Combined) (Table 14.2.1.17.25 through Table 14.2.1.17.28). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.18 Blood WBC Tables

Number	Title	Shell
Table 14.2.1.18.1	Summary of Blood WBC (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.18.2	Summary of Blood WBC (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.18.3	Summary of Blood WBC Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.18.4	Statistical Comparisons of Blood WBC (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.18.5	Statistical Comparisons of Blood WBC (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.18.6 through Table 14.2.1.18.10), for the CEMA-compliant Biomarker Population (Table 14.2.1.18.11 through Table 14.2.1.18.14), for the MITT Biomarker Population (Combined) (Table 14.2.1.18.15 through Table 14.2.1.18.19), for the PP Biomarker Population (Combined) (Table 14.2.1.18.20 through Table 14.2.1.18.24), and for the CEMA-compliant Biomarker Population (Combined) (Table 14.2.1.18.25 through Table 14.2.1.18.28). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.19 Blood HDL-C Tables

Number	Title	Shell
Table 14.2.1.19.1	Summary of Blood HDL-C (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.19.2	Summary of Blood HDL-C (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.19.3	Summary of Blood HDL-C Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.19.4	Statistical Comparisons of Blood HDL-C (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.19.5	Statistical Comparisons of Blood HDL-C (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.19.6 through Table 14.2.1.19.10), for the CEMA-compliant Biomarker Population (Table 14.2.1.19.11 through Table 14.2.1.19.14), for the MITT Biomarker Population (Combined) (Table 14.2.1.19.15 through Table 14.2.1.19.19), for the PP Biomarker Population (Combined) (Table 14.2.1.19.20 through Table 14.2.1.19.24), and for the CEMA-compliant Biomarker Population (Combined) (Table 14.2.1.19.25 through Table 14.2.1.19.28). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.20 Urine 11-DTX-B2 Tables

Number	Title	Shell
Table 14.2.1.20.1	Summary of Urine 11-DTX-B2 Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.20.2	Summary of Urine 11-DTX-B2 Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.20.3	Summary of Urine 11-DTX-B2 Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.20.4	Summary of Urine 11-DTX-B2 Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.20.5	Summary of Urine 11-DTX-B2 Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.20.6	Summary of Urine 11-DTX-B2 Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.20.7	Statistical Comparisons of Urine 11-DTX-B2 Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.20.8	Statistical Comparisons of Urine 11-DTX-B2 Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.20.9 through Table 14.2.1.20.16), for the CEMA-compliant Biomarker Population (Table 14.2.1.20.17 through Table 14.2.1.20.23), for the MITT Biomarker Population (Combined) (Table 14.2.1.20.24 through Table 14.2.1.20.31), for the PP Biomarker Population (Combined) (Table 14.2.1.20.32 through Table 14.2.1.20.39), and for the CEMA-compliant Biomarker Population (Combined) (Table 14.2.1.20.40 through Table 14.2.1.20.46). There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.1.21 Urine 8-epi-PGF2alpha Tables

Number	Title	Shell
Table 14.2.1.21.1	Summary of Urine 8-epi-PGF2alpha Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.21.2	Summary of Urine 8-epi-PGF2alpha Amount Excreted (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.21.3	Summary of Urine 8-epi-PGF2alpha Amount Excreted Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.21.4	Summary of Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.21.5	Summary of Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine (unit) Absolute Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1
Table 14.2.1.21.6	Summary of Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine Percent Change From Baseline by Arm and Visit (MITT Biomarker Population)	CBSum1

Number	Title	Shell
Table 14.2.1.21.7	Statistical Comparisons of Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)	CBStat1
Table 14.2.1.21.8	Statistical Comparisons of Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)	CBStat2

Similar tables will be included for the PP Biomarker Population (Table 14.2.1.21.9 through Table 14.2.1.21.16), for the CEMA-compliant Biomarker Population (Table 14.2.1.21.17 through Table 14.2.1.21.23), for the MITT Biomarker Population (Combined) (Table 14.2.1.21.24 through Table 14.2.1.21.31), the PP Biomarker Population (Combined) (Table 14.2.1.21.32 through Table 14.2.1.21.39), and for the CEMA-compliant Biomarker Population (Combined) (Table 14.2.1.21.40 through Table 14.2.1.21.46).. There will be no Day 5 statistical comparison tables for CEMA-compliant population.

14.2.2 Biomarker Figures

14.2.2.1 Urine NNAL Figures

Number	Title	Shell
Figure 14.2.2.1.1	Mean (SD) Urine NNAL Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.1.2	Mean (SD) Urine NNAL Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.1.3	Mean (SD) Urine NNAL Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.1.4	Mean (SD) Urine NNAL Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.1.5	Box Plot of Urine NNAL Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Number	Title	Shell
Figure 14.2.2.1.6	Box Plot of Urine NNAL Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.1.7	Box Plot of Urine NNAL Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.1.8	Box Plot of Urine NNAL Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.1.9 through Figure 14.2.2.1.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.1.17 through Figure 14.2.2.1.24).

14.2.2.2 Urine NNN Figures

Number	Title	Shell
Figure 14.2.2.2.1	Mean (SD) Urine NNN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.2.2	Mean (SD) Urine NNN Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.2.3	Mean (SD) Urine NNN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.2.4	Mean (SD) Urine NNN Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.2.5	Box Plot of Urine NNN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.2.6	Box Plot of Urine NNN Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.2.7	Box Plot of Urine NNN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.2.8	Box Plot of Urine NNN Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.2.9 through Figure 14.2.2.2.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.2.17 through Figure 14.2.2.2.24).

14.2.2.3 Urine 2-MHBMA Figures

Number	Title	Shell
Figure 14.2.2.3.1	Mean (SD) Urine 2-MHBMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.3.2	Mean (SD) Urine 2-MHBMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.3.3	Mean (SD) Urine 2-MHBMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.3.4	Mean (SD) Urine 2-MHBMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.3.5	Box Plot of Urine 2-MHBMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.3.6	Box Plot of Urine 2-MHBMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.3.7	Box Plot of Urine 2-MHBMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.3.8	Box Plot of Urine 2-MHBMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.3.9 through Figure 14.2.2.3.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.3.17 through Figure 14.2.2.3.24).

14.2.2.4 Urine 3-HPMA Figures

Number	Title	Shell
Figure 14.2.2.4.1	Mean (SD) Urine 3-HPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1

Number	Title	Shell
Figure 14.2.2.4.2	Mean (SD) Urine 3-HPMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.4.3	Mean (SD) Urine 3-HPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.4.4	Mean (SD) Urine 3-HPMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.4.5	Box Plot of Urine 3-HPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.4.6	Box Plot of Urine 3-HPMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.4.7	Box Plot of Urine 3-HPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.4.8	Box Plot of Urine 3-HPMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.4.9 through Figure 14.2.2.4.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.4.17 through Figure 14.2.2.4.24).

14.2.2.5 Urine SPMA Figures

Number	Title	Shell
Figure 14.2.2.5.1	Mean (SD) Urine SPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.5.2	Mean (SD) Urine SPMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.5.3	Mean (SD) Urine SPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.5.4	Mean (SD) Urine SPMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.5.5	Box Plot of Urine SPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Number	Title	Shell
Figure 14.2.2.5.6	Box Plot of Urine SPMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.5.7	Box Plot of Urine SPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.5.8	Box Plot of Urine SPMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.5.9 through Figure 14.2.2.5.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.6.17 through Figure 14.2.2.6.24).

14.2.2.6 Urine HEMA Figures

Number	Title	Shell
Figure 14.2.2.6.1	Mean (SD) Urine HEMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.6.2	Mean (SD) Urine HEMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.6.3	Mean (SD) Urine HEMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.6.4	Mean (SD) Urine HEMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.6.5	Box Plot of Urine HEMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.6.6	Box Plot of Urine HEMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.6.7	Box Plot of Urine HEMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.6.8	Box Plot of Urine HEMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.6.9 through Figure 14.2.2.6.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.6.17 through Figure 14.2.2.6.24).

14.2.2.7 Urine 1-AN Figures

Number	Title	Shell
Figure 14.2.2.7.1	Mean (SD) Urine 1-AN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.7.2	Mean (SD) Urine 1-AN Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.7.3	Mean (SD) Urine 1-AN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.7.4	Mean (SD) Urine 1-AN Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.7.5	Box Plot of Urine 1-AN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.7.6	Box Plot of Urine 1-AN Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.7.7	Box Plot of Urine 1-AN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.7.8	Box Plot of Urine 1-AN Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.7.9 through Figure 14.2.2.7.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.7.17 through Figure 14.2.2.7.24).

14.2.2.8 Urine 2-AN Figures

Number	Title	Shell
Figure 14.2.2.8.1	Mean (SD) Urine 2-AN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.8.2	Mean (SD) Urine 2-AN Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1

Number	Title	Shell
Figure 14.2.2.8.3	Mean (SD) Urine 2-AN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.8.4	Mean (SD) Urine 2-AN Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.8.5	Box Plot of Urine 2-AN Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.8.6	Box Plot of Urine 2-AN Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.8.7	Box Plot of Urine 2-AN Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.8.8	Box Plot of Urine 2-AN Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.8.9 through Figure 14.2.2.8.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.8.17 through Figure 14.2.2.8.24).

14.2.2.9 Urine CEMA Figures

Number	Title	Shell
Figure 14.2.2.9.1	Mean (SD) Urine CEMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.9.2	Mean (SD) Urine CEMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.9.3	Mean (SD) Urine CEMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.9.4	Mean (SD) Urine CEMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.9.5	Box Plot of Urine CEMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.9.6	Box Plot of Urine CEMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Number	Title	Shell
Figure 14.2.2.9.7	Box Plot of Urine CEMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.9.8	Box Plot of Urine CEMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.9.9 through Figure 14.2.2.9.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.9.17 through Figure 14.2.2.9.24).

14.2.2.10 Urine 3-OH-B[a]P Figures

Number	Title	Shell
Figure 14.2.2.10.1	Mean (SD) Urine 3-OH-B[a]P Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.10.2	Mean (SD) Urine 3-OH-B[a]P Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.10.3	Mean (SD) Urine 3-OH-B[a]P Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.10.4	Mean (SD) Urine 3-OH-B[a]P Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.10.5	Box Plot of Urine 3-OH-B[a]P Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.10.6	Box Plot of Urine 3-OH-B[a]P Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.10.7	Box Plot of Urine 3-OH-B[a]P Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.10.8	Box Plot of Urine 3-OH-B[a]P Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.10.9 through Figure 14.2.2.10.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.10.17 through Figure 14.2.2.10.24).

14.2.2.11 Urine HMPMA Figures

Number	Title	Shell
Figure 14.2.2.11.1	Mean (SD) Urine HMPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.11.2	Mean (SD) Urine HMPMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.11.3	Mean (SD) Urine HMPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.11.4	Mean (SD) Urine HMPMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.11.5	Box Plot of Urine HMPMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.11.6	Box Plot of Urine HMPMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.11.7	Box Plot of Urine HMPMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.11.8	Box Plot of Urine HMPMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.11.9 through Figure 14.2.2.11.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.11.17 through Figure 14.2.2.11.24).

14.2.2.12 Urine 4-ABP Figures

Number	Title	Shell
Figure 14.2.2.12.1	Mean (SD) Urine 4-ABP Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.12.2	Mean (SD) Urine 4-ABP Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.12.3	Mean (SD) Urine 4-ABP Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1

Number	Title	Shell
Figure 14.2.2.12.4	Mean (SD) Urine 4-ABP Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.12.5	Box Plot of Urine 4-ABP Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.12.6	Box Plot of Urine 4-ABP Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.12.7	Box Plot of Urine 4-ABP Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.12.8	Box Plot of Urine 4-ABP Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.12.9 through Figure 14.2.2.12.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.12.17 through Figure 14.2.2.12.24).

14.2.1.13 Urine SBMA Figures

Number	Title	Shell
Figure 14.2.2.13.1	Mean (SD) Urine SBMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.13.2	Mean (SD) Urine SBMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.13.3	Mean (SD) Urine SBMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.13.4	Mean (SD) Urine SBMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.13.5	Box Plot of Urine SBMA Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.13.6	Box Plot of Urine SBMA Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.13.7	Box Plot of Urine SBMA Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Number	Title	Shell
Figure 14.2.2.13.8	Box Plot of Urine SBMA Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.13.9 through Figure 14.2.2.13.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.13.17 through Figure 14.2.2.13.24).

14.2.2.14 Blood COHb Figures

Number	Title	Shell
Figure 14.2.2.14.1	Mean (SD) Blood COHb (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.14.2	Mean (SD) Blood COHb Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.14.3	Box Plot of Blood COHb (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.14.4	Box Plot of Blood COHb Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.14.5 through Figure 14.2.2.14.8) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.14.9 through Figure 14.2.2.14.12).

14.2.2.15 Urine NE Figures

Number	Title	Shell
Figure 14.2.2.15.1	Mean (SD) Urine NE Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.15.2	Mean (SD) Urine NE Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.15.3	Mean (SD) Urine NE Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.15.4	Mean (SD) Urine NE Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.15.5	Box Plot of Urine NE Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Number	Title	Shell
Figure 14.2.2.15.6	Box Plot of Urine NE Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.15.7	Box Plot of Urine NE Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.15.8	Box Plot of Urine NE Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.15.9 through Figure 14.2.2.15.16) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.15.17 through Figure 14.2.2.15.24).

14.2.2.16 Blood CEVal Figures

Number	Title	Shell
Figure 14.2.2.16.1	Mean (SD) Blood CEVal (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.16.2	Mean (SD) Blood CEVal Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.16.3	Box Plot of Blood CEVal (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.16.4	Box Plot of Blood CEVal Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.16.5 through Figure 14.2.2.16.8) and for the CEMA-compliant Biomarker Population (Figure 14.2.2.16.9 through Figure 14.2.2.16.12).

14.2.2.17 Blood sICAM-1 Figures

Number	Title	Shell
Figure 14.2.2.17.1	Mean (SD) Blood sICAM-1 (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.17.2	Mean (SD) Blood sICAM-1 Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.17.3	Box Plot of Blood sICAM-1 (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Number	Title	Shell
Figure 14.2.2.17.4	Box Plot of Blood sICAM-1 Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.17.5 through Figure 14.2.2.17.8), for the CEMA-compliant Biomarker Population (Figure 14.2.2.17.9 through Figure 14.2.2.17.12), for the MITT Biomarker Population (Combined) (Figure 14.2.2.17.13 through Figure 14.2.2.17.16), for the PP Biomarker Population (Combined) (Figure 14.2.2.17.17 through Figure 14.2.2.17.20), and for the CEMA-compliant Biomarker Population (Combined) (Figure 14.2.2.17.21 through Figure 14.2.2.17.24).

14.2.2.18 Blood WBC Figures

Number	Title	Shell
Figure 14.2.2.18.1	Mean (SD) Blood WBC (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.18.2	Mean (SD) Blood WBC Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.18.3	Box Plot of Blood WBC (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.18.4	Box Plot of Blood WBC Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.18.5 through Figure 14.2.2.18.8), for the CEMA-compliant Biomarker Population (Figure 14.2.2.18.9 through Figure 14.2.2.18.12), for the MITT Biomarker Population (Combined) (Figure 14.2.2.18.13 through Figure 14.2.2.18.16), for the PP Biomarker Population (Combined) (Figure 14.2.2.18.17 through Figure 14.2.2.18.20), and for the CEMA-compliant Biomarker Population (Combined) (Figure 14.2.2.18.21 through Figure 14.2.2.18.24)..

14.2.2.19 Blood HDL-C Figures

Number	Title	Shell
Figure 14.2.2.19.1	Mean (SD) Blood HDL-C (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.19.2	Mean (SD) Blood HDL-C Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.19.3	Box Plot of Blood HDL-C (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Number	Title	Shell
Figure 14.2.2.19.4	Box Plot of Blood HDL-C Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.19.5 through Figure 14.2.2.19.8), for the CEMA-compliant Biomarker Population (Figure 14.2.2.19.9 through Figure 14.2.2.19.12), for the MITT Biomarker Population (Combined) (Figure 14.2.2.19.13 through Figure 14.2.2.19.16), for the PP Biomarker Population (Combined) (Figure 14.2.2.19.17 through Figure 14.2.2.19.20), and for the CEMA-compliant Biomarker Population (Combined) (Figure 14.2.2.19.21 through Figure 14.2.2.19.24)..

14.2.2.20 Urine 11-DTX-B2 Figures

Number	Title	Shell
Figure 14.2.2.20.1	Mean (SD) Urine 11-DTX-B2 Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.20.2	Mean (SD) Urine 11-DTX-B2 Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.20.3	Mean (SD) Urine 11-DTX-B2 Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.20.4	Mean (SD) Urine 11-DTX-B2 Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.20.5	Box Plot of Urine 11-DTX-B2 Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.20.6	Box Plot of Urine 11-DTX-B2 Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.20.7	Box Plot of Urine 11-DTX-B2 Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.20.8	Box Plot of Urine 11-DTX-B2 Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.20.9 through Figure 14.2.2.20.16), for the CEMA-compliant Biomarker Population (Figure 14.2.2.20.17 through Figure 14.2.2.20.24), for the MITT Biomarker Population (Combined) (Figure 14.2.2.20.25 through Figure 14.2.2.20.32), for the PP Biomarker Population (Combined) (Figure 14.2.2.20.33 through Figure 14.2.2.20.40), and for the CEMA-compliant Biomarker Population (Combined) (Figure 14.2.2.20.41 through Figure 14.2.2.20.48).

14.2.2.21 Urine 8-epi-PGF2alpha Figures

Number	Title	Shell
Figure 14.2.2.21.1	Mean (SD) Urine 8-epi-PGF2alpha Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.21.2	Mean (SD) Urine 8-epi-PGF2alpha Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.21.3	Mean (SD) Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.21.4	Mean (SD) Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBFig1
Figure 14.2.2.21.5	Box Plot of Urine 8-epi-PGF2alpha Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.21.6	Box Plot of Urine 8-epi-PGF2alpha Amount Excreted Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.21.7	Box Plot of Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1
Figure 14.2.2.21.8	Box Plot of Urine 8-epi-PGF2alpha Adjusted for Urine Creatinine Change From Baseline (unit) by Arm and Visit (MITT Biomarker Population)	CBBox1

Similar figures will be included for the PP Biomarker Population (Figure 14.2.2.21.9 through Figure 14.2.2.21.16), for the CEMA-compliant Biomarker Population (Figure 14.2.2.21.17 through Figure 14.2.2.21.24), for the MITT Biomarker Population (Combined) (Figure 14.2.2.21.25 through Figure 14.2.2.21.32), for the PP Biomarker Population (Combined) (Figure 14.2.2.21.33 through Figure 14.2.2.21.40), and for the CEMA-compliant Biomarker Population (Combined) (Figure 14.2.2.21.41 through Figure 14.2.2.21.48).

14.2.3 Subjective Assessment Tables

Number	Title	Shell
Table 14.2.3.1	Summary of Modified Cigarette Effects Questionnaire by Arm and Visit (Subjective Measures Population)	CBSum1

14.2.4 Subjective Assessment Figures

Number	Title	Shell
Figure 14.2.4.1	Mean (SD) Modified Cigarette Effects Questionnaire (Product Use Satisfaction) by Arm and Visit (Subjective Measures Population)	CBFig1
Figure 14.2.4.2	Mean Modified Cigarette Effects Questionnaire (Product Use Satisfaction) by Arm and Visit (Subjective Measures Population)	CBFig2
Figure 14.2.4.3	Mean (SD) Modified Cigarette Effects Questionnaire (Psychological Reward) by Arm and Visit (Subjective Measures Population)	CBFig1
Figure 14.2.4.4	Mean Modified Cigarette Effects Questionnaire (Psychological Reward) by Arm and Visit (Subjective Measures Population)	CBFig2
Figure 14.2.4.5	Mean (SD) Modified Cigarette Effects Questionnaire (Aversion) by Arm and Visit (Subjective Measures Population)	CBFig1
Figure 14.2.4.6	Mean Modified Cigarette Effects Questionnaire (Aversion) by Arm and Visit (Subjective Measures Population)	CBFig2
Figure 14.2.4.7	Mean (SD) Modified Cigarette Effects Questionnaire (Enjoyment of the Sensation) by Arm and Visit (Subjective Measures Population)	CBFig1
Figure 14.2.4.8	Mean Modified Cigarette Effects Questionnaire (Enjoyment of the Sensation) by Arm and Visit (Subjective Measures Population)	CBFig2
Figure 14.2.4.9	Mean (SD) Modified Cigarette Effects Questionnaire (Craving Reduction) by Arm and Visit (Subjective Measures Population)	CBFig1
Figure 14.2.4.10	Mean Modified Cigarette Effects Questionnaire (Craving Reduction) by Arm and Visit (Subjective Measures Population)	CBFig2

14.2.5 Product Use Tables

Number	Title	Shell
Table 14.2.5.1	Summary of Daily Product Consumption During the Confinement Phase by Arm and Visit (Product Use Population)	CBSum1
Table 14.2.5.2	Summary of Average Daily Product Consumption During the Ambulatory Phase by Arm and Visit (Product Use Population)	CBSum1

14.2.6 Product Use Figures

Number	Title	Shell
Figure 14.2.6.1	Mean (SD) Daily Product Consumption During the Confinement Phase by Arm and Visit (Product Use Population)	CBFig1
Figure 14.2.6.2	Mean Daily Product Consumption During the Confinement Phase by Arm and Visit (Product Use Population)	CBFig2
Figure 14.2.6.3	Mean (SD) Average Daily Product Consumption During the Ambulatory Phase by Arm and Visit (Product Use Population)	CBFig1
Figure 14.2.6.4	Mean Average Daily Product Consumption During the Ambulatory Phase by Arm and Visit (Product Use Population)	CBFig2

14.2.7 Respiratory Symptom Experience Scale Tables

Number	Title	Shell
Table 14.2.7.1	Summary of Respiratory Symptom Experience Scale Composite Score by Arm and Visit (Safety Population)	CBSum1
Table 14.2.7.2	Summary of Respiratory Symptom Experience Scale Composite Score Change From Baseline by Arm and Visit (Safety Population)	CBSum1
Table 14.2.7.3	Statistical Comparisons of Respiratory Symptom Experience Scale Composite Score Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (Safety Population)	CBStat2

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Number	Title	Shell
Table 14.3.1.1	Product Use-Emergent Adverse Event Frequency by Arm – Number of Subjects Reporting the Event (% of Subjects Dosed) (Product Trial and Safety Population)	CAES
Table 14.3.1.2	Product Use -Emergent Adverse Event Frequency by Arm – Number of Adverse Events (% of Total Adverse Events) (Product Trial and Safety Population)	CAEE
Table 14.3.1.3	Product Use-Emergent Adverse Event Frequency by Arm, Severity, and Relationship to Study Product – Number of Adverse Events (Product Trial and Safety Population)	CAESR

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Number	Title	Shell
Table 14.3.2.1	Serious Adverse Events (Safety Population)	16.2.7

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each subject)

Number	Title	Shell
Table 14.3.4.1	Out-of-Range Values and Recheck Results – Chemistry (Safety Population)	CLBO
Table 14.3.4.2	Out-of-Range Values and Recheck Results – Hematology (Safety Population)	
Table 14.3.4.3	Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)	

14.3.5 Displays of Vital Signs and Other Safety Data

Number	Title	Shell
Table 14.3.5.1	Vital Sign Summary (Safety Population)	CVS
Table 14.3.5.2	Spirometry and Change From Baseline Summary (Safety Population)	CSP

10.2 Section 16 Data Listings

Note: Hepatitis and HIV results that are provided by the clinical laboratory will not be presented in subject data listings and will not be included in any database transfer. All data will be presented as outline in the eCRF (i.e., time point information will be consistent with the CRF data).

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

16.1.9 Statistical Methods

Number	Title
Appendix 16.1.9.1	Statistical Analysis Plan
Appendix 16.1.9.2	Statistical Methods – Biomarkers

16.1.10 Clinical Laboratory Reference Ranges

Number	Title
Appendix 16.1.10	Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Number	Title
Appendix 16.2.1.1	Subject Disposition (Enrolled Population)

16.2.2 Protocol Deviations

Number	Title
Appendix 16.2.2.1	Protocol Deviations

16.2.3 Subjects Excluded From the Biomarker Analysis

Number	Title
Appendix 16.2.3.1	Subjects Excluded From the Biomarker Analysis

Note: Appendix 16.2.3.1 is generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Number	Title
Appendix 16.2.4.1	Demographics (Enrolled Population)
Appendix 16.2.4.2	Reproductive Status (Enrolled Population)
Appendix 16.2.4.3	Physical Examination (Enrolled Population)
Appendix 16.2.4.4	Medical History (Enrolled Population)
Appendix 16.2.4.5	Usual Brand Attribute – Cigarette (Enrolled Population)
Appendix 16.2.4.6	Fagerstrom Test for Cigarette Dependence (Enrolled Population)

16.2.5 Compliance and/or Blood and Urine Sample Collection Data

Number	Title
Appendix 16.2.5.1	Inclusion/Exclusion Criteria (Enrolled Population)
Appendix 16.2.5.2	Study Visit (Enrolled Population)
Appendix 16.2.5.3	Subject Status (Enrolled Population)
Appendix 16.2.5.4	Check-in Product Trial (Product Trial and Safety Population)
Appendix 16.2.5.5	Cigarette Use (Day -2 Through Day -1) (Product Trial and Safety Population)
Appendix 16.2.5.6	Randomization (Randomized Population)
Appendix 16.2.5.7	Product Administration During the Confinement Phase (Safety Population)
Appendix 16.2.5.8	Study Product Compliance During the Ambulatory Phase (Safety Population)
Appendix 16.2.5.9	Product Home Use (Safety Population)
Appendix 16.2.5.10	Prior and Concomitant Medications (Safety Population)
Appendix 16.2.5.11	Blood Sampling for BoE, BoPH and CEVal (Safety Population)
Appendix 16.2.5.12	24-Hour Urine Collection (Safety Population)

16.2.6 Individual Biomarker/Subjective Assessment/Daily Product Use Data

Number	Title	Shell
Appendix 16.2.6.1	Urine NNAL (Safety Population)	UBLIS
Appendix 16.2.6.2	Urine NNN (Safety Population)	UBLIS

Number	Title	Shell
Appendix 16.2.6.3	Urine 2-MHBMA (Safety Population)	UBLIS
Appendix 16.2.6.4	Urine 3-HPMA (Safety Population)	UBLIS
Appendix 16.2.6.5	Urine SPMA (Safety Population)	UBLIS
Appendix 16.2.6.6	Urine HEMA (Safety Population)	UBLIS
Appendix 16.2.6.7	Urine 1-AN (Safety Population)	UBLIS
Appendix 16.2.6.8	Urine 2-AN (Safety Population)	UBLIS
Appendix 16.2.6.9	Urine CEMA (Safety Population)	UBLIS
Appendix 16.2.6.10	Urine 3-OH-B[a]P (Safety Population)	UBLIS
Appendix 16.2.6.11	Urine HMPMA (Safety Population)	UBLIS
Appendix 16.2.6.12	Urine 4-ABP (Safety Population)	UBLIS
Appendix 16.2.6.13	Urine SBMA (Safety Population)	UBLIS
Appendix 16.2.6.14	Blood COHb (Safety Population)	BBLIS
Appendix 16.2.6.15	Urine Nicotine and Metabolites (Safety Population)	UBLIS2
Appendix 16.2.6.16	Urine NE (Safety Population)	UBLIS
Appendix 16.2.6.17	Blood CEVal (Safety Population)	BBLIS
Appendix 16.2.6.18	Blood sICAM-1 (Safety Population)	BBLIS
Appendix 16.2.6.19	Blood WBC (Safety Population)	BBLIS
Appendix 16.2.6.20	Blood HDL-C (Safety Population)	BBLIS
Appendix 16.2.6.21	Urine 11-DTX-B2 (Safety Population)	UBLIS
Appendix 16.2.6.22	Urine 8-epi-PGF2alpha (Safety Population)	UBLIS
Appendix 16.2.6.23	Modified Cigarette Effects Questionnaire - Questions	MCEQQLIS
Appendix 16.2.6.24	Modified Cigarette Effects Questionnaire – Original Response (Safety Population)	MCEQOLIS
Appendix 16.2.6.25	Modified Cigarette Effects Questionnaire – Factor Scores (Safety Population)	MCEQFLIS
Appendix 16.2.6.26	Modified Cigarette Effects for Heated Tobacco Product Questionnaire - Questions	MCEQQLIS
Appendix 16.2.6.27	Modified Cigarette Effects for Heated Tobacco Product Questionnaire – Original Response (Safety Population)	MCEQOLIS

Number	Title	Shell
Appendix 16.2.6.28	Modified Cigarette Effects for Heated Tobacco Product Questionnaire – Factor Scores (Safety Population)	MCEQFLIS
Appendix 16.2.6.29	Daily Product Consumption During the Confinement Phase (Safety Population)	DPCCLIS
Appendix 16.2.6.30	Respiratory Symptom Experience Scale Assessments (Safety Population)	RSELIS

16.2.7 Adverse Events Listings

Number	Title
Appendix 16.2.7.1	Adverse Events (Safety Population)
Appendix 16.2.7.2	Details for Serious Adverse Events (Safety Population) *This listing will be removed if no serious adverse events are reported.*
Appendix 16.2.7.3	Heated Tobacco Product Issues (Safety Population)

16.2.8 Clinical Laboratory Reports

Number	Title
Appendix 16.2.8.1	Clinical Laboratory Report - Chemistry (Safety Population)
Appendix 16.2.8.2	Clinical Laboratory Report - Hematology (Safety Population)
Appendix 16.2.8.3	Clinical Laboratory Report - Urinalysis (Safety Population)
Appendix 16.2.8.4	Alcohol, Drug, and Cotinine Screen (Safety Population)
Appendix 16.2.8.5	Serology (Safety Population)
Appendix 16.2.8.6	Pregnancy (Safety Population)
Appendix 16.2.8.7	Vital Signs (Safety Population)
Appendix 16.2.8.8	12-Lead Electrocardiogram (Safety Population)
Appendix 16.2.8.9	Spirometry (Safety Population)
Appendix 16.2.8.10	Exhaled Carbon Monoxide (Safety Population)

11. TABLE, FIGURE, AND LISTING SHELLS

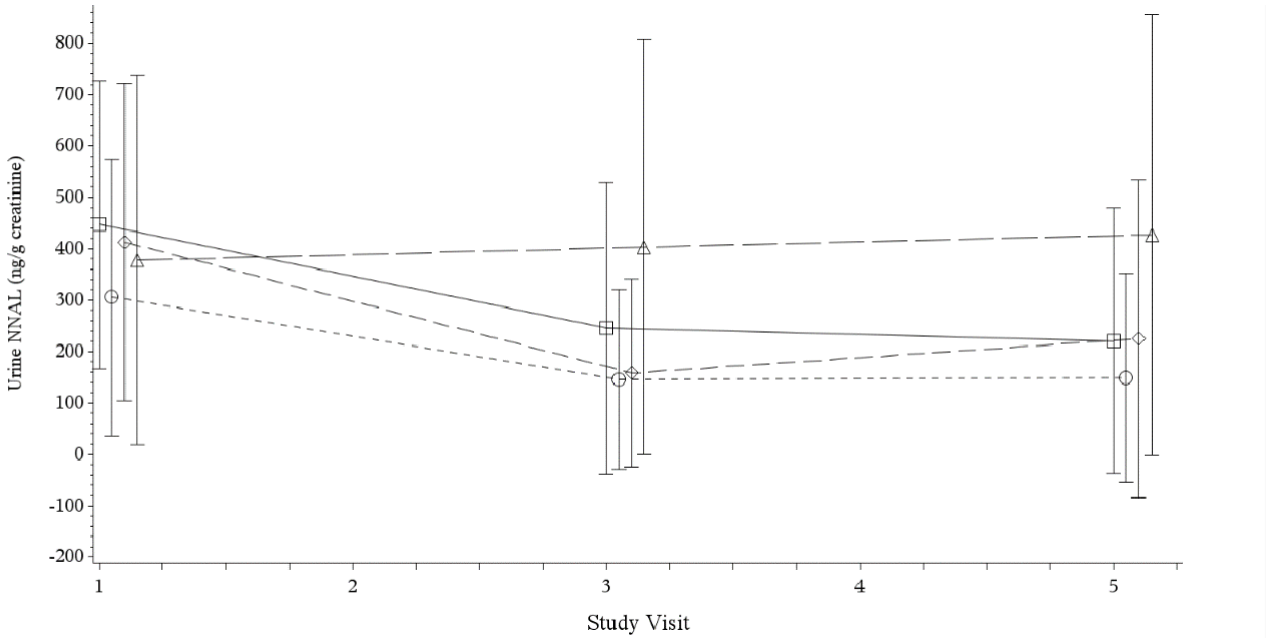
The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. Unless otherwise noted, all tables will be presented in Times New Roman font size 9. All tables and figures will be generated as RTF document for inclusion in the CSR. In compliance with [redacted] PGs/SOPs, SAS® outputs will not be manually edited. Tables and figures will be generated from ADaM datasets created in accordance with CDISC guidance (ADaM Model 2.1 and ADaM implementation Guide 1.1).

Source datasets will be added as footnotes in each table.

11.1 Figures Shells

Mean (SD) graphs will be in the following format:

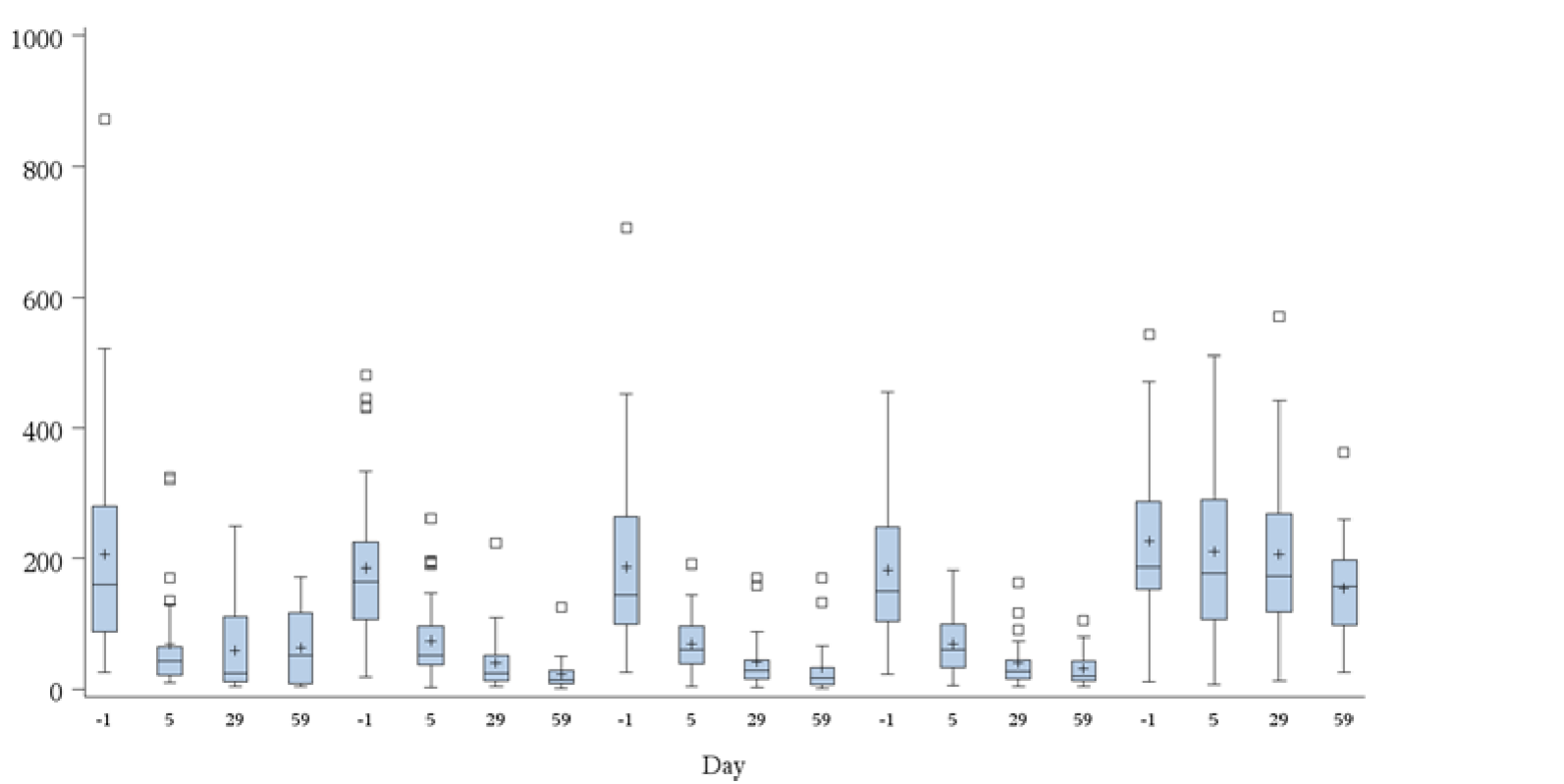
Figure CBFig1 Mean (SD) Urine NNAL Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)



Programmer note: There will be 6 lines for the 6 arms and Arms 2-6 will be shifted to the right for ease of reading. The study visit will be Day -1, Day 5, Day 30 and Day 60. The change from baseline and percent change from baseline will not have Day -1 timepoint.

All Box plots will have the following format:

Figure CBBox1 Box Plot of Urine NNAL Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)



Programmer note: The x-axis will be study visit with Days -1, 5, 30, and 60 for each arm. There are 6 arms and the order of the box will be by study visit and then arm. Each visit will be labeled above the six study arms for the visit. Color plots (one color per arm) to be created using SGPLOT (or another appropriate) SAS procedure. There will be 24 boxes for original values and 18 boxed for change from baseline.

11.2 Section 14 Summary Tables Shells

Table CDS Summary of Disposition (Enrolled/Product Trial/Randomized/Safety/MITT/PP/CEMA Compliant Biomarker Populations)

			Group 1 (Menthol)				Group 2 (Non-menthol)				
Population	Category	Product Trial*	Arm 1	Arm 2	Arm 3	Overall	Arm 4	Arm 5	Arm 6	Overall	Overall#
Enrolled	Screen Failure	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Enrolled	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Randomized/Assigned	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Not Randomized	X	X	X	X	X	X	X	X	X	X
	<Reason1>	X	X	X	X	X	X	X	X	X	X
	<Reason2>	X	X	X	X	X	X	X	X	X	X
	Completed Study	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Discontinued Early	X	X	X	X	X	X	X	X	X	X
	<Reason1>	X	X	X	X	X	X	X	X	X	X
	<Reason2>	X	X	X	X	X	X	X	X	X	X
Product Trial	Enrolled	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Randomized/Assigned	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Not Randomized	X	X	X	X	X	X	X	X	X	X
	<Reason1>	X	X	X	X	X	X	X	X	X	X
	<Reason2>	X	X	X	X	X	X	X	X	X	X
	Completed Study	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Discontinued Early	X	X	X	X	X	X	X	X	X	X
	<Reason1>	X	X	X	X	X	X	X	X	X	X
	<Reason2>	X	X	X	X	X	X	X	X	X	X

<Programmer note: Randomized/Safety/MITT/PP/CEMA Compliant Biomarker Populations will also be presented in the table. Product trial column will be blank for MITT/PP/CEMA Compliant Biomarker Populations.>

Arm X: < >
MITT = Modified intend-to-treat; PP = Per protocol
* Only includes subjects who participated in the product trial, but dropped from the study prior to the start of product use on Day 1.
# Subjects who only participated in the product trail are excluded from overall column.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab prog_name.sas DDMMMYYYY HH:MM

Table CDM Demographic Summary (Safety/MITT/PP/CEMA Compliant Populations)

			Group 1 (Menthol)				Group 2 (Non-menthol)				
Population	Trait		Arm 1	Arm 2	Arm 3	Overall	Arm 4	Arm 5	Arm 6	Overall	Overall#
Safety	Sex	Male	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
		Female	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	Race	American Indian	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
		Asian	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
		Black	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	Age (yr)	n	X	X	X	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Weight (kg)	n	X	X	X	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX

<Programmer note: Also include ethnicity, Height, and BMI as well as the summary for MITT/PP/CEMA Compliant population. Also add "Product Trial column as in CDS shell with column header as "Product Trial*".>

Arm X: < >
MITT = Modified intend-to-treat; PP = Per protocol
BMI = Body mass index
* Only includes subjects who participated in the product trial, but dropped from the study prior to the start of product use on Day 1.
# Subjects who only participated in the product trail are excluded from overall column.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table CTNH Tobacco and Nicotine Product Use Summary (Safety/MITT/PP/CEMA Compliant Populations)

			Group 1 (Menthol)				Group 2 (Non-menthol)				
Population	Trait	Answer	Arm 1	Arm 2	Arm 3	Overall	Arm 4	Arm 5	Arm 6	Overall	Overall#
Safety	Number of Years Smoked	n	X	X	X	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Average CPD Smoked	n	X	X	X	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX

<Programmer note: Also include the summary for MITT/PP/CEMA Compliant population. Also add "Product Trial column as in CDS shell with column header as "Product Trial*".>

Arm X: < >
MITT = Modified intend-to-treat; PP = Per protocol; CPD = Cigarettes per day
* Only includes subjects who participated in the product trial, but dropped from the study prior to the start of product use on Day 1.
# Subjects who only participated in the product trail are excluded from overall column.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table CUB Usual Brand Summary (Safety/MITT/PP/CEMA Compliant Population)

			Group 1 (Menthol)				Group 2 (Non-menthol)				
Population	Trait		Arm 1	Arm 2	Arm 3	Overall	Arm 4	Arm 5	Arm 6	Overall	Overall#
Safety	Brand	XXXXXXX	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
		XXXXXXXX	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
		XXXXXXXXXX	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	Flavor	Menthol	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
		Non-Menthol	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)

<Programmer note: Also include the summary for MITT/PP/CEMA Compliant population. Also add "Product Trial column as in CDS shell with column header as "Product Trial*.>

Arm X: < >
MITT = Modified intend-to-treat; PP = Per protocol
* Only includes subjects who participated in the product trial, but dropped from the study prior to the start of product use on Day 1.
# Subjects who only participated in the product trail are excluded from overall column.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.1.5 FTCD Score Summary (Safety/MITT/PP/CEMA Compliant Populations)

		Group 1 (Menthol)				Group 2 (Non-menthol)				
Population	Statistic	Arm 1	Arm 2	Arm 3	Overall	Arm 4	Arm 5	Arm 6	Overall	Overall
Safety	n	X	X	X	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX
MITT	n	X	X	X	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX

<Programmer note: Also include the summary for PP/CEMA Compliant population. Also add “Product Trial column as in CDS shell with column header as “Product Trial*”.>

Arm X: < >

FTCD =

Fagerstorm test for cigarette dependence which is the sum of all individual item scores.
MITT = Modified intend-to-treat; PP = Per protocol
* Only includes subjects who participated in the product trial, but dropped from the study prior to the start of product use on Day 1.
# Subjects who only participated in the product trail are excluded from overall column.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table CBSum1 Summary of Urine NNAL Amount Excreted (unit) by Arm and Visit (MITT Biomarker Population)

			Arm					
Visit	Sex	Statistic	1	2	3	4	5	6
Day -1	Female	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV%	X.X	X.X	X.X	X.X	X.X	X.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Q1	X.X	X.X	X.X	X.X	X.X	X.X
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Q3	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX
	Male	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV%	X.X	X.X	X.X	X.X	X.X	X.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Q1	X.X	X.X	X.X	X.X	X.X	X.X
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Q3	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX

<Programmer note: Sex should also include Overall across sexes. Visit should also include Days 5, 30, and 60. There is no Day -1 for absolute and percent change from baseline tables. Geometric means will also be presented for the original data. For the combined flavor tables, there will be three columns for HTP, Continue Smoking, and Smoking Abstinence. >

Arm X: < >

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer note: For daily product consumption tables, there will be no columns for Arm 3 and Arm 6 after Day -1.

Table CBStat1 Statistical Comparisons of Urine NNAL Adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 5 (MITT Biomarker Population)

Visit	Comparison	LS Means Test (n)	LS Means Reference (n)	LS Mean Difference (Test – Reference)	95% Confidence Interval	p-value
Day 5	Arm 1 vs Arm 2	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 1 vs Arm 3	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 4 vs Arm 5	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 4 vs Arm 6	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

Arm X: < >
The mixed model includes Arm, sex, and CPD strata as fixed effects, site as a random effect, and age and Baseline biomarker value as the covariates.
Data from Arms 1-6 are included in the analysis. The analysis is performed for each group separately.
Test = First Arm in the comparison; Reference = Second Arm in the comparison
n = Number of observations used in the analysis; Least-squares means (LS Means) are calculated from the model.
MITT = Modified intend-to-treat

Program: /CAXXXXX/sas_prg/pksas PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer note: If sex effect is statistically significant ($p < 0.05$), the LSMeans for each sex will be calculated and the results will be in the SAS outputs.

Table CBStat2 Statistical Comparisons of Urine NNAL adjusted for Urine Creatinine (unit) Change From Baseline Between HTP Arms and Continue Smoking Arms and Between HTP Arms and Smoking Abstinence Arms on Day 30 and Day 60 (MITT Biomarker Population)

Visit	Comparison	LS Means Test (n)	LS Means Reference (n)	LS Mean Difference (Test – Reference)	95% Confidence Interval	p-value
Day 30	Arm 1 vs Arm 2	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 1 vs Arm 3	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 4 vs Arm 5	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 4 vs Arm 6	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
Day 60	Arm 1 vs Arm 2	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 1 vs Arm 3	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 4 vs Arm 5	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Arm 4 vs Arm 6	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

Arm X: < >
The mixed model includes Arm, sex, visit, CPD strata, and arm by visit as fixed effects, site as a random effect, and age and Baseline biomarker values as the covariates.
Data from Arms 1-6 are included in the analysis. The analysis is performed for each group separately.
Test = First Arm in the comparison; Reference = Second Arm in the comparison
n = Number of observations used in the analysis; Least-squares means (LS Means) are calculated from the model.
MITT = Modified intend-to-treat

Program: /CAXXXXX/sas_prg/pksas PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer note: If sex effect is statistically significant ($p < 0.05$), the LSMeans for each sex will be calculated and the results will be in the SAS outputs.

Table CAES Product Use-Emergent Adverse Event Frequency by Arm – Number of Subjects Reporting the Event (% of Subjects Dosed)
(Product Trial and Safety Population)

		Arm						
Adverse Event*	Product Trial#	1	2	3@	4	5	6@	Overall
Number of Subjects Who Received Study Product	XXX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)
Number of Subjects With Adverse Events	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Number of Subjects Without Adverse Events	XXX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Cardiac disorders	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Palpitations	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Vomiting	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)

Arm X: <>
*Adverse events are classified according to MedDRA Version 26.0.
#Product trial include the adverse events occurred during the product trial and baseline period.
^Adverse events occurred during the product trial period are excluded from Overall summary.
@For subjects in Smoking Abstinence arms, the post use AEs are counted from Day 1 morning when the subjects in the other arms started to use study prducts.

Program: /CAXXXXX/sas_prg/pksas/pdproduse/adam_programname.sas DDMMMYYYY HH:MM

Table CAEE Product Use –Emergent Adverse Event Frequency by Arm – Number of Adverse Events (% of Total Adverse Events)
(Product Trial and Safety Population)

		Arm						
Adverse Event*	Product Trial#	1	2	3@	4	5	6@	Overall
Number of PUEAEs	XXX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)
Cardiac disorders	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Palpitations	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)
Vomiting	X (X%)	X (XX%)	X (X%)	XX (XX%)	X (X%)	X (X%)	X (X%)	X (X%)

Arm X: <>
*Adverse events are classified according to MedDRA Version 26.0.
#Product trial include the adverse events occurred during the product trial and baseline period.
^Adverse events occurred during the product trial period are excluded from Overall summary.
@For subjects in Smoking Abstinence arms, the post use AEs are counted from Day 1 morning when the subjects in the other arms started to use study prducts.

Program: /CAXXXXX/sas_prg/pksas/pdproduse/adam_programname.sas DDMMMYYYY HH:MM

Table CAESR Product Use-Emergent Adverse Event Frequency by Arm, Severity, and Relationship to Study Product – Number of Adverse Events
(Product Trial and Safety Population)

Adverse Event*	Arm	Number of Subjects with Adverse Events	Severity			Relationship to Study Product				
			Mild	Moderate	Severe	Not Related	Unlikely	Possibly	Likely	Definitely
Back pain	X	X	X	X	X	X	X	X	X	X
Blood glucose increased	X	X	X	X	X	X	X	X	X	X
COVID-19	X	X	X	X	X	X	X	X	X	X
Chest discomfort	X	X	X	X	X	X	X	X	X	X
Cough	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X
Dyspepsia	X	X	X	X	X	X	X	X	X	X
Dyspnoea	X	X	X	X	X	X	X	X	X	X
Headache	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X
	X	X	X	X	X	X	X	X	X	X
Product Trial#		X	X	X	X	X	X	X	X	X
Arm 1		X	X	X	X	X	X	X	X	X
Arm 2		X	X	X	X	X	X	X	X	X
Arm 3@		X	X	X	X	X	X	X	X	X
Arm 4		X	X	X	X	X	X	X	X	X
Arm 5		X	X	X	X	X	X	X	X	X
Arm 6@		X	X	X	X	X	X	X	X	X
Overall^		X	X	X	X	X	X	X	X	X

Cohort X: < >
*Adverse events are classified according to MedDRA Version 26.0.
#Product trial include the adverse events occurred during the product trial and baseline period.
^Adverse events occurred during the product trial period are excluded from Overall summary.
@For subjects in Smoking Abstinence arms, the post use AEs are counted from Day 1 morning when the subjects in the other arms started to use study prducts.

Program: /CAXXXXX/sas_prg/pksas/pdproduse/adam_programname.sas DDMMMYYYY HH:MM

Table 14.3.2.1 Serious Adverse Events (Safety Population)

There were no serious adverse events recorded during the study

<Programmer Note: If there are SAEs, the table will resemble Appendix 16.2.7.2.>

Program: /CAXXXXX/sas_prg/stsas/tab cdash_tblae_ser.sas DDMMMYYYY HH:MM

Table CLBO Out-of-Range Values and Recheck Results - Serum Chemistry (Safety Population)

Subject Number	Age/ Sex	Study Visit	Arm	Date	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)	Parameter5 <Range> (Unit)
X	XX/X	Screen	X	DDMMMYYYY	XX HN				XX HN
X	XX/X	Screen	X	DDMMMYYYY		XX HN	XX HN	XX LN	

< Programmer Notes: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early termination chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for.>

Arm X: < >
H = Above reference range, L = Below reference range

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table CVS Vital Sign Summary (Safety Population)

Vital Sign (units)	Time Point	Statistic	Arm 1	2	3	4	5	6
Testname (unit)	Baseline	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX
	Day 6	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX

< Similar for and remaining vital signs measurements and time points. >

Arm X : < >
Baseline is the last non-missing values prior to randomization/Assignment (usually Day -2).

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.3.5.13 Spirometry Summary (Safety Population)

Parameter (units)	Time Point		Statistic	Arm 1	2	3	4	5	6
Testname (unit)	Baseline	Measured	n	X	X	X	X	X	X
			Mean	X.X	X.X	X.X	X.X	X.X	X.X
			SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			Minimum	XX	XX	XX	XX	XX	XX
			Median	X.X	X.X	X.X	X.X	X.X	X.X
			Maximum	XX	XX	XX	XX	XX	XX
	Day 60	Measured	n	X	X	X	X	X	X
			Mean	X.X	X.X	X.X	X.X	X.X	X.X
			SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			Minimum	XX	XX	XX	XX	XX	XX
			Median	X.X	X.X	X.X	X.X	X.X	X.X
			Maximum	XX	XX	XX	XX	XX	XX
		Change	n	X	X	X	X	X	X
			Mean	X.X	X.X	X.X	X.X	X.X	X.X
			SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			Minimum	XX	XX	XX	XX	XX	XX
			Median	X.X	X.X	X.X	X.X	X.X	X.X
			Maximum	XX	XX	XX	XX	XX	XX

< Similar for and remaining spirometry parameters. >

Arm X : < >
Baseline is the last non-missing values prior to randomization/Assignment (usually Screening).

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

11.3 Listing Shells

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final report. Listings will be generated from data created in accordance with SDTM Model 1.7 with Implementation Guide 3.3 or higher or CDASH data structure. Listings with derived data (i.e., amount excreted for urine biomarkers, etc.) may be created from the ADaM data. All listings will be presented in Times New Roman font size 9. Time point information will match that found in the CRF.

Source datasets will be added as footnotes in each listing.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Reference Range	Unit
Serum Chemistry	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
Hematology	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units
	Test Name	<>	<>	XX - XX	units

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Similar for remaining Laboratory Groups and Test Names. If there are multiple clinical laboratories performed the laboratory tests, the site column will be added to the listing as the first column.

Appendix 16.2.1.1 Subject Disposition (Enrolled Population)

Subject Number	Arm	Completion/ Discontinuation Date	Subject's Status	Specify Reason for Subject Status	Reason For Not Randomized
X	X	DDMMMYYYY	XXX		XXXXX
X	X	DDMMMYYYY	XX		
X	X	DDMMMYYYY	XX		
X	X	DDMMMYYYY	XX		
X	X	DDMMMYYYY	XXX	XXXXXXXXXXXX	
X	X	DDMMMYYYY	XX		
X	X	DDMMMYYYY	XX		
X	X	DDMMMYYYY	XX		

Arm X: < >
AE = Adverse event

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.1 Demographics (Enrolled Population)

Subject Number	Arm	Year of Birth	Age (yr)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	Informed Consent Date
X	X	XXXX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	X	XXXX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	X	XXXX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	X	XXXX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	X	XXXX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	X	XXXX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY
X	X	XXXX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY

Arm X: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2 Reproductive Status (Enrolled Population)

Subject Number	Menopausal Status	Child-bearing Potential	Contraception Method Used	Postmenopausal Status Confirmed by FSH Test	Date of the FSH Sample Collection
X	XXXXXXXXX	XXXXX	XXXXXX	XXX	DDMMMYYYY

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.3 Physical Examination (Enrolled Population)

Subject Number	Study Visit	Was PE Performed?	Reason for Not Done	Date	Were All Required Findings From the PE Entered as Medical History?
X	Screening	XXX		DDMMMYYYY	XXXXXX

PE = Physical examination

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.4 Medical History (Enrolled Population)

Subject Number	Any History?	Study Visit	Condition or Event Term	Start Date	Ongoing?	End Date	If Ongoing, are Concomitant Medications Being Taken?	MH Start Year
X	XXX	Screen	XXXXXXXXXXX	DDMMMYYYY	Yes		XXXX	YYYY
			XXXXXXXXXXX	DDMMMYYYY	No	DDMMMYYYY		YYYY

MH = Medical history;

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.5 Usual Brand Attribute – Cigarette (Enrolled Population)

Subject Number	Study Visit	Usual Cigarette Brand	Other, Specify	Flavor	UPC Code	Color Image Obtained?	Average Cigarettes Smoked per Day	Years Smoked Cigarettes
X	Screening	XXXXXXXXX		Menthol	XXXXXXXXXX	Yes	XX	XX

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.6 Fagerstrom Test for Cigarette Dependence (Enrolled Population)

Subject Number	Study Visit	Was Assessment Completed?	Date	Time	Question* 1	2	3	4	5	6	Total Score
X	XXX	XXX	DDMMMYYYY	HH:MM	XXXXXXXX	XXX	XXX	XX	XXXXXXXX	XXX	XXX

*Question Descriptions:
1 = How soon after you wake up do you smoke your first cigarette?
2 = Do you find it difficult to refrain from smoking in places where it is forbidden (e.g. church, library, at the movies, etc.)?
3 = Which cigarette would you hate most to give up?
4 = How many cigarettes per day do you smoke?
5 = Do you smoke more frequently during the first hours after waking than during the rest of the day?
6 = Do you smoke if you are so ill that you are in bed most of the day?

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.1 Inclusion/Exclusion Criteria (Enrolled Population)

Subject Number	Study Visit	Were all Eligibility Criteria Met?	Inclusion Criterion not Met or Exclusion Criterion Met
X	Screening	Yes	XXX
X	Screening	Yes	XXX

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2 Study Visit (Enrolled Population)

Subject Number	Study Visit	Visit date
X	Screening	DDMMMYYYY

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2 Subject Status (Enrolled Population)

Subject Number	Study Visit	Visit Date	Question	Answer
X	Check-in	DDMMMYYYY	Did the subject participate in the product trial at Check-In Day -2?	Yes
	Day 6	DDMMMYYYY	Did the subject continue to the ambulatory phase of the study?	Yes

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4 Product Trial Check-in Product Trial (Product Trial and Safety Population)

Subject Number	Study Visit	Product Dispensed	Amount Dispensed	Date for Product Trial	Start Time	End Time	Used Product Collected	Specify Reason not Collected
X	XXX	XXXXXXX	XX	DDMMMYYYY	HH:MM	HH:MM	Yes	

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.5 Cigarette Use (Day -2 Through Day -1) (Product Trial and Safety Population)

Subject Number	Study Visit	Date	Product Dispensed	Amount Dispensed	Start Time	End Time	Used Product Collected	Specify Reason not Collected
X	XXX	DDMMMYYYY	XXXXXXX	XX	HH:MM	HH:MM	Yes	
					HH:MM	HH:MM	No	XXXXX
					HH:MM	HH:MM	Yes	

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.6 Randomization (Randomized Population)

Subject Number	Study Visit	Date of Randomization	Was the Subject's Assigned Group	CPD Stratification	Sex	Randomization Number	Product Code	Product
X	XXX	DDMMMYYYY	Menthol	High	XXXX	XXXX	XXXX	XXXXXXXX

CPD = Cigarettes per day

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.7 Product Administration During the Confinement Phase (Safety Population)

Subject Number	Arm	Visit	Product Code	Product Assigned	Date	Product Dispensed	Amount Dispensed	Start Time	End Time	Used Product Collected	Specify Reason not Collected
X	X	Day X	XXX	XXXXXX	DDMMMYYYY	XXXXXXX	1 Stick	HH:MM	HH:MM	Yes	
						XXXXXXX	1 Stick	HH:MM	HH:MM	No	XXXXXXX
						XXXXXXX	1 Stick	HH:MM	HH:MM	Yes	
	X	Day X	XXX	XXXXXX	DDMMMYYYY	XXXXXXX	1 Stick	HH:MM	HH:MM	Yes	
						XXXXXXX	1 Stick	HH:MM	HH:MM	Yes	
						XXXXXXX	1 Stick	HH:MM	HH:MM	Yes	

Arm X: < >

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.8 Study Product Compliance During the Ambulatory Phase (Safety Population)

Subject Number	Visit	Arm	Product Assigned	Report HTP Used Per Day?*	Report Cigarette Used Per Day?#	Product Used	How Product Used@	Average Amount Used^
X	Day X	X	XXXXXX	XXX	XXX	XXXXXX	Every Day	XXXX
						XXXXXX	Some Day	XXXX

Arm X: < >
* Over the past two weeks, what was the subject reported HTP use per day?
# Over the past two weeks, what was the subject reported cigarette use per day
@ How was the product used since the last visit?
^ On the days the product was used, what was the average amount used?

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Page 1 of X

Appendix 16.2.5.9 Product Home Use (Safety Population)

Subject Number	Arm	Dispense Visit	Study Product Dispensed	Date Product Dispensed	Number of Sticks Dispensed	Return Visit	Number of Sticks Returned	Was All Product Returned?	Reason For Not Return	Re-Supply	Date Product Re-Supply	Number of Sticks Re-Dispensed
X	X	Day 6	XXXXXX	DDMMMYYYY	XXXX	XXX	XXX	XXX		X	DDMMMYYYY	XXXX
		Day 15	XXXXXX	DDMMMYYYY	XXXX	XXX	XXX	XXX				
		Day 30	XXXXXX	DDMMMYYYY	XXXX	XXX	XXX	XXX		X	DDMMMYYYY	XXXX
		Day 45	XXXXXX	DDMMMYYYY	XXXX	XXX	XXX	XXX				

Arm X: < >

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.10 Prior and Concomitant Medications (Safety Population)

Subject Number	Arm	Any ConMed Taken?	Medication/ Therapy Name (WHO Term)	Start Date	Ongoing	End Date	Dosage	Frequency	Route	Indication	Related MH and AE
X	X	XXX	XXXXXXXXXX (XXXXXXX)	DDMMMYYYY	Yes		XX mg	XXXX	XXXX	XXXX	XXXXXXX

Arm X: < >
*Concomitant medications are coded with WHO Dictionary Version 01MAR2023 B3.
MH = Medical history; AE = Adverse event

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.11 Blood Sampling for BoE, BoPH and CEVal (Safety Population)

Subject Number	Arm	Study Visit	Lab Test	Was Blood Sample Collected?	Date of Collection	Time of Collection
X	X	XXXX	CARBOXYHEMOGLOBIN	XXX	DDMMMYYYY	HH:MM
			BIOMARKERS of POTENTIAL HARM (BoPH)	XXX	DDMMMYYYY	HH:MM
			CEVal	XXX	DDMMMYYYY	HH:MM
		XXXX	CARBOXYHEMOGLOBIN	XXX	DDMMMYYYY	HH:MM
			BIOMARKERS of POTENTIAL HARM (BoPH)	XXX	DDMMMYYYY	HH:MM
			CEVal	XXX	DDMMMYYYY	HH:MM
		XXXX	CARBOXYHEMOGLOBIN	XXX	DDMMMYYYY	HH:MM
			BIOMARKERS of POTENTIAL HARM (BoPH)	XXX	DDMMMYYYY	HH:MM
			CEVal	XXX	DDMMMYYYY	HH:MM

Arm X: < >

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.12 24-Hour Urine Collection (Safety Population)

Subject Number	Arm	Study Visit	Was the Sample Collected?	Reason for Not Collected	Start Date	Start Time	End Date	End Time	Total Weight (g)	Number of Void	Any Voids Incomplete, Lost or Discarded
X	X	XXXX	XXX		DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	XXX	X	No
		XXXX	XXX		DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	XXX	X	No
		XXXX	XXX		DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	XXX	X	No
		XXXX	XXX		DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	XXX	X	No

Arm X: < >

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix UBLIS Urine NNAL (Safety Population)

Subject Number	Arm	Visit	NNAL (pg/mL)	Urine Weight (g)	NNAL (ng/24 hours)	NNAL (ng/24 hours) Change	NNAL (ng/24 hours) % Change	NNAL (ng/mg creatinine)	NNAL (ng/mg creatinine) Change	NNAL (ng/mg creatinine) % Change	MITT Flag	PP Flag	CEMA Flag
X	X	Day -1	XXX	XXX	XXX	NA	NA	XXX	NA	NA	Y	Y	Y
		Day 5	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	Y	Y	Y
		Day 30	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	Y	Y	Y
		Day 60	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	Y	Y	Y

Arm X: <>
Day -1 is typically the baseline measurement.
NA = Not applicable; MITT = Modified intend-to-treat; PP = Per Protocol; CEMA = CEMA-compliant

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix UBLIS2 Urine Nicotine Metabolites

Subject Number	Arm	Study Visit	Nicotine (ng/mL)	Nicotine Glucuronide (ng/mL)	Cotinine (ng/mL)	Cotinine Glucuronide (ng/mL)	Trans-3-hydroxy Cotinine (ng/mL)	Trans-3-hydroxy Cotinine Glucuronide (ng/mL)
X	X	Day -1	XXX	XXX	XXX	XXX	XXX	XXX
		Day 5	XXX	XXX	XXX	XXX	XXX	XXX
		Day 30	XXX	XXX	XXX	XXX	XXX	XXX

Arm X: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix BBLIS Blood COHb

Subject Number	Arm	Study Visit	COHb (% sat)	COHb ------(% sat)-------- Change	COHb ------(% sat)-------- % Change	MITT Flag	PP Flag	CEMA Flag
X	X	Day -1	XXX	NA	NA	Y	Y	Y
		Day 5	XXX	XXX	XXX	Y	Y	Y
		Day 30	XXX	XXX	XXX	Y	Y	Y
		Day 60	XXX	XXX	XXX	Y	Y	Y

Arm X: <>
Day -1 is typically the baseline measurement.
NA = Not applicable; MITT = Modified intend-to-treat; PP = Per Protocol; CEMA = CEMA-compliant

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix MCEQQLIS Modified Cigarette Effects Questionnaire - Questions

1. Was smoking cigarettes satisfying?
2. Did the cigarettes taste good?
3. Did you enjoy the sensations 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 youenjoy smoking cigarettes?

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix NCEQOLIS Modified Cigarette Effects Questionnaire – Original Response (Safety Population)

Subject Number	Arm	Study Visit	Was mCEQ Completed?	Date	Time	Question 1	2	3	4	5	6	7	8	9	10	11	12
X	X	XXXX	Yes	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	X	X	X	X

Arm X: < >
Scale: 1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = a lot, 6 = quite a lot, 7 = extremely
Refer to Appendix 16.2.6.23 for description of questions.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix NCEQFLIS Modified Cigarette Effects Questionnaire – Factor Scores (Safety Population)

Subject Number	Arm	Study Visit	Date	Time	Product Use Satisfaction	Psychological Reward	Aversion	Enjoyment of the Sensation	Craving Reduction
X	X	XXXX	DDMMMYYYY	HH:MM	X.X	X.X	X.X	X	X

Arm X: < >
Product use satisfaction: average of the response scores from Questions 1, 2, and 12;
Psychological reward: average of the response scores from Questions 4 to 8;
Aversion: average of the response scores from Questions 9 and 10;
Enjoyment of the sensation: response score from Question 3;
Craving reduction: response score from Question 11.
Scale: 1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = a lot, 6 = quite a lot, 7 = extremely

Refer to Appendix 16.2.6.23 for description of questions.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix DPCCLIS Daily Product Consumption During the Confinement Phase (Safety Population)

Subject Number	Arm	Study Visit	Date	Product	Number of HTP Sticks Used or Number of Cigarettes Smoked
X	X	XXXX	DDMMMYYYY	XXXXX	XXXX

Arm X: < >
Number of HTP Sticks Used or Number of Cigarettes Smoked is derived from product administration during the confinement phase (Appendix 16.2.5.7).

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix RSELIS Respiratory Symptom Experience Scale Assessments (Safety Population)

Subject Number	Arm	Study Visit	Was RSE Scale Completed?	Date	Time	Question 1	2	3	4	5	Composite Score
X	X	XXXX	Yes	DDMMMYYYY	HH:MM	XXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXX	XX

Arm X: < >
RSE = Respiratory symptom experience
1. Morning cough with phlegm or mucus
2. Cough frequently throughout the day
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
4. Becoming easily winded during normal daily activities (eg, doing laundry and carrying groceries)
5. Wheezing or whistling in your chest at times when you are not exercising or doing other physically strenuous daily activities (eg, while resting)

Score: 1 = Never (0 days out of the last 30 days); 2 = Rarely (1-5 days); 3 = Occasionally (6-15 days); 4 = Most days (16-29 days); 5 = Every day (all 30 days out of the last 30 days)
Composite score is calculated by taking the average of the 5 RSES items.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.1 Adverse Events (Safety Population)

Subject Number	Age/ Sex	Arm	PUE?	System Organ Class/ Preferred Term (Verbatim)	Time From Last Use (DD:HH:MM)	Date:Time Start/ End Duration (DD:HH:MM) Ongoing?	Serious/ Outcome/ Severity	Study Product Relationship/ Action	ConMed Given/ Caused Discontinuation	Cause Death/ Date
1	30/F			None						
2	24/M			None						
3	52/M	X	Yes	XXXXXXXXXXXX/ XXXXXXXXXXXXXXXX (XXXXXXXXXXXX)	XX:XX:XX	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15/ XXXXXX	No/ Recovered/ Resolved/ Mild	Related/ Product Use Withdrawn	XXX/ XXXX	No
		X	Yes	<similar to above>						

Arm X: < >
Adverse events are classified according to MedDRA Version 26.0.
PUE = Abbreviation for product use-emergent; ConMed = Concomitant medication
F = Female; M = Male

Programmer Note: AEs should be presented start date/time order for each subject.

Program: /CAXXXXX/sas_prg/stsas/lis/programname.sas DDMONYYYY HH:MM

Appendix 16.2.7.2 Details for Serious Adverse Events (Safety Population)

Subject Sex	Age/	Arm	PUE?	System Organ Class/ Preferred Term (Verbatim)	Date:Time Start/ End Duration (DD:HH:MM) Ongoing?	Serious Event?	Congenital Anomaly/ Birth Defect?	Persistent or Significant Disability or Incapacity?	Hospital-ization?	Life-Threat?	Important Medical Event?	Number Death
1	30/F			None								
2	24/M			None								
3	52/M	X	Yes	XXXXXXXXXXX/ XXXXXXXXXXXXXXXXX (XXXXXXXXXXX)	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15/ XXXXX	Yes	No	No	Yes	No	Yes: < >	No

Arm X: < >
Adverse events are classified according to MedDRA Version 26.0.
PUE = Abbreviation for product use-emergent
F = Female; M = Male

Programmer Note: If Serious = Yes then present AEs in this listing otherwise please do not include this listing.

Program: /CAXXXXX/sas_prg/stsas/lis/programname.sas DDMONYYYY HH:MM

Appendix 16.2.7.3 Heated Tobacco Product Issues (Safety Population)

Subject Number	Arm	Study Visit	Any Issue?	Heated Tobacco Product Issue	Date of Event or Issue	Pattern of Issue	Action Taken With Device
X	X	XXXX	XXX	XXXX	DDMMMYYYY	Single Event	No Action Taken

Arm X: < >

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendices 16.2.8.1.1 to 16.2.8.1.3 will have the following format.

Appendix 16.2.8.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)

Subject Number	Age/ Sex	Arm	Study Visit	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)	Parameter6 < Range> (Unit)
X	XX	X	Screening	DDMMMYYYY	XX H	XX	XX	XX	XX H	XX

Arm X: <>
H = Above reference range; L = Below reference range

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study.

Appendix 16.2.8.4 Alcohol, Drug, and Cotinine Screen (Safety Population)

Subject Number	Arm	Study Visit	Lab Test	Date	Result	Laboratory Name	Specimen Type	Test Not Performed
X	X	Screening	ALCOHOL SCREEN	DDMMMYYYY	XXX	XXXXXX	XXXX	
			DRUG SCREEN	DDMMMYYYY	XXX	XXXXXX	XXXX	
			COTININE	DDMMMYYYY	XXX	XXXXXX	XXXX	

Arm X: < >

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.5 Serology (Safety Population)

Subject Number	Study Visit	Was Serology Test Performed?	Date of Collection
X	Screening	XXX	DDMMMYYYY

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.6 Pregnancy Test (Safety Population)

Subject Number	Study Visit	Was the Pregnancy Test Performed?	Date of Test	Specimen Type	Result	Laboratory Name
X	Screening	XXX	DDMMMYYYY	XXXXXX	XXXXXX	XXXXXXXXX

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.7 Vital Signs (Safety Population)

Subject Number	Arm	Study Visit	Was VS Performed?	Date	Time	Blood Pressure (mmHg) Systolic/Diastolic	Heart Rate (bpm)	Respiratory (rpm)	Temperature (°C)	Weight (kg)
X	X	Screening	XXX	DDMMMYYYY	X:XX	XXX/ XX	XX	XX	XX.X	XXX.X
		X	XXX	DDMMMYYYY	XX:XX	XXX/ XX	XX	XX	XX.X	

Arm X: < >
VS = Vital sign

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.8 12-Lead Electrocardiogram (Safety Population)

Subject Number	Study Visit	Was ECG Performed	Date	Time	Interpretation	Specify Abnormal Assessment	Clinically Significant?
X	Screening	XXX	DDMMMYYYY	HH:MM	XXXXXXX	XXXXXXXXXX	No

ECG = Electrocardiogram

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.9 Spirometry (Safety Population)

Subject Number	Study Visit	Arm	Test Event*	Done?	Date	Time	FEF 25-75% (L/sec)	FEV1 (L)	FVC (L)	Peak Expiratory Flow (L/sec)
X	Screening	X	XXX	XXX	DDMMMYYYY	HH:MM	XX	XX	XX	XX
			XXXX	XXX	DDMMMYYYY	HH:MM	XX	XX	XX	XX

Arm X: < >
FEF 25-75% = Forced Expiratory Flow 25-75%; FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity
*pre = pre-bronchodilator; post = post-bronchodilator

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.10 Expired Carbon Monoxide (Safety Population)

Subject Number	Arm	Study Visit	Was Expired CO Test Performed?	Lab Test	Date of Test	Result (ppm)	Laboratory Name
X	X	Screening	XXX	CARBON MONOXIDE	DDMMMYYYY	XX	XXXXXXXXXXXX

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

12. REFERENCE

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addictive Behaviors. 2007;32(5):912-923.

Haziza, Christelle, et al. "Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the menthol tobacco heating system 2.2 for 3 months (Part 1)." *Nicotine and Tobacco Research* 22.4 (2020): 539-548.

Shiffman S, McCaffrey, S, Hannon M, Goldenson N, Black R. A New Questionnaire to Assess Respiratory Symptoms (The Respiratory Symptom Experience Scale): Quantitative Psychometric Assessment and Validation Study. JMIR Form Res 2023 | vol. 7 | e44036