[redacted]

16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

[redacted]

STATISTICAL ANALYSIS PLAN

A single-center, randomized, controlled, open-label study in smoking healthy subjects to investigate the nicotine pharmacokinetic profiles following single use of Tobacco Heating System (THS) with a regular or a menthol stick, compared to smoking of a single combustible cigarette (CIG)

Short Title: Nicotine pharmacokinetics of THS single use of a regular or a menthol stick compared to CIG

Protocol No: P1-PK-12
Protocol Version 1.0 Date: 22 November 2022
Protocol Version 2.0 (Protocol Amendment) Date: 06 February 2023
Test Product Name: Tobacco Heating System (THS) Induction device and regular or menthol sticks

[redacted] Project CA39924
Final Version 1.0
Date: 15 March 2023

Philip Morris Products S.A.
Quai Jeanrenaud 3
2000 Neuchâtel, Switzerland

[redacted]

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Test Product Name: Tobacco Heating System (THS) Induction device and regular or menthol sticks

Protocol: P1-PK-12

Study Title: A single-center, randomized, controlled, open-label study in smoking healthy subjects to investigate the nicotine pharmacokinetic profiles following single use of Tobacco Heating System (THS) with a regular or a menthol stick, compared to smoking of a single combustible cigarette (CIG)

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Issue Date: 15 March 2023

Signature: DocuSigned by: [redacted] Signing Reason: I approve this document Signing Time: 16-Mar-2023 | 15:04:18 GMT C78FAC5F913745B6B7514D09F8A8CA64 Date: _____

[redacted], MS
Principal Scientist, Biostatistics, Data Management and Biometrics
[redacted]

Signature: DocuSigned by: [redacted] Signing Reason: I approve this document Signing Time: 16-Mar-2023 | 14:42:19 GMT 3D6AF47F39BD44F0872CA6D388D93769 Date: _____

[redacted], DPharm, DESS
Principal Scientist, Clinical Pharmacology and Pharmacometrics
Data Management and Biometrics
[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 the Philip Morris Products S.A., will be considered out of scope and must be described in the CSR.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To describe the plasma concentration-time profile of nicotine and derived pharmacokinetic (PK) parameters of a single use of THS with either a regular or a menthol stick or of a single combustible cigarette (CIG)	Plasma nicotine concentration-time PK parameters (THS regular stick, THS menthol stick, and CIG separately): • Maximum nicotine plasma concentration [Cmax] • Time to the maximum nicotine plasma concentration [Tmax] • Area under the curve of nicotine plasma concentration-time computed from T0 to T=24 hours [AUC0-24h] • Area under the curve of nicotine plasma concentration-time computed from T0 to the subject-specific time of maximum nicotine concentration [AUC0-Tmax]

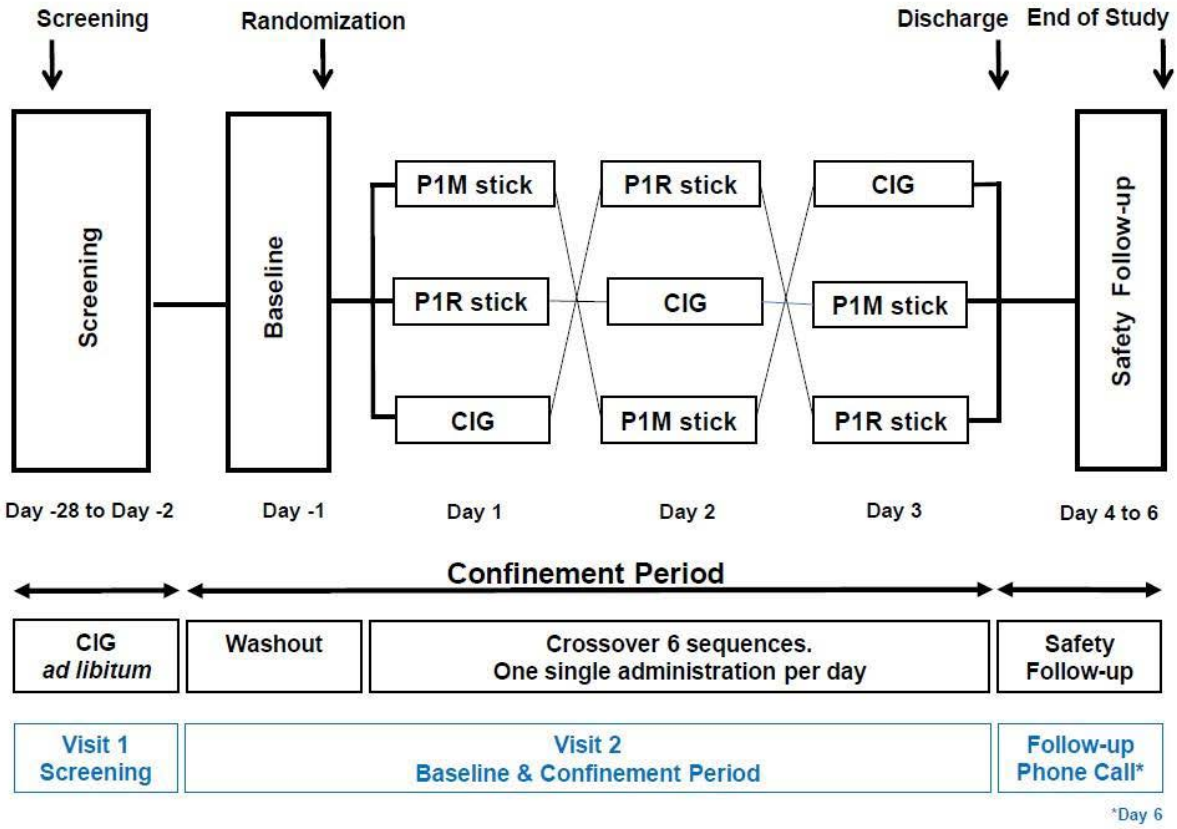
Secondary	
To evaluate pharmacodynamic (PD) effects (subjective effects) of a single use of a THS with either a regular or a menthol stick or of a single CIG.	• Score of CIG craving by the visual analogue scale (VAS) Craving assessment • Score of investigational product (IP) liking by the VAS Liking assessment • Score of intention to use the IP again by the VAS Intention to Use Again assessment
To evaluate the safety of test products during the study.	• Incidence of adverse events (AEs) and serious adverse events (SAEs) • Incidence of product events • Changes in electrocardiogram (ECG) from baseline (heart rate, PR, QRS, QT, QTcF interval) • Changes in vital signs from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate) • Concomitant medication • Changes in standard spirometry from baseline (FEV1, FEV1 % predicted, FVC, FVC % predicted, FEV1/FVC) • Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel

3. STUDY DESIGN

This study is designed to meet the objectives outlined in Section 2.

This is a single-center, randomized, controlled, open-label, cross-over study in healthy subjects. The study will be conducted with 3 periods and 6 sequences in a cross-over design.

Figure 1 Study Design



Abbreviations: CIG = combustible cigarette; P1M = menthol taste; P1R = regular taste

A Screening visit will be conducted within 27 days (Day -28 to Day -2) prior to admission (on Baseline Day -1) to the investigational site (Figure 1) to check and document the eligibility of the subjects. Investigational site staff will demonstrate the THS (without product use) during the Screening visit. The brand of subjects' cigarettes will be recorded.

Qualified subjects will return to the investigational site for Baseline on Day -1. Subjects will have fasted for at least 6 hours prior to the safety laboratory assessments. After confirmation of eligibility, subjects can be randomized. All subjects who will not be randomized will be documented as screen failures.

Thirty subjects will be randomized to one of 6 possible full crossover sequences of IP use (THS with either regular or menthol stick, and CIG) on Day 1 to Day 3 (see Figure 1). After admission on Baseline Day -1 in the morning, nicotine wash-out will start, and the use of any other tobacco and/or nicotine containing products (TNP) different from the IP assigned for use on Day 1 to Day 3, will not be allowed. Use of TNP will not be restricted after the subject has been discharged from the investigational site on Day 3.

On Day 1 to Day 3, after at least 23 hours of abstinence from any TNP on Day 1, and after at least 24 hours of former IP use on Day 2 and Day 3 (nicotine wash-out), subjects will smoke a single CIG or perform a single use of a THS either with a regular or a menthol stick, according to randomized product use sequence.

The start of IP use will be defined as T_0. T_0 on Day 1 to Day 3 should be at approximately the same time in the morning. Venous blood samples will be obtained according to the standard operating procedures (SOPs) at the investigational site. Subjects will report their cigarette craving, IP liking, and intention to use again by performing VAS assessments.

After Discharge on Day 3 or after Early termination following product exposure, the subjects will enter a 3-day Safety follow-up (SFU) period during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs will be conducted, concluded per a telephone contact by the investigational site on the last day of the SFU period.

4. ANALYSIS POPULATIONS

4.1 Screened Population

The screened population consists of all subjects who underwent at least one screening procedure.

4.2 Safety Population (SAF)

The safety population is a subset of the screened population and consists of all subjects who give informed consent and have at least one safety assessment.

4.3 Randomized Population

The randomized population is a subset of the safety population and consists of all the subjects who were randomized at Baseline (Day -1). Subjects for which inclusion/exclusion criteria were violated or subject for which the documentation for eligibility was incomplete at time of enrolment will be excluded from this population.

4.4 Pharmacokinetic Population

The PK population is a subset of the randomized population and consists of all randomized subjects for whom at least one nicotine PK parameter can be derived. This population will also be applied for the PD parameters. Only subjects without major protocol deviations (see Section 4.4.1) which have an impact on evaluability of the main objective will be included in the PK population.

4.4.1 Protocol Deviations

Protocol deviations are considered as deviations from the study procedures as defined in the study protocol, including but not limited to, as any violation of inclusion/exclusion criteria, mis-randomizations, assessments not performed or performed outside the scheduled time

windows, or use of drugs that are known to affect components of the "smokers' health profile."

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Subjects with major protocol deviations will be identified to determine whether they will be excluded from any of the analysis populations.

Major deviations will include but are not limited to the deviations presented in Table 4.1.

Table 4.1 Definition of Major Protocol Deviations Categories

Sub-Category	Description
Protocol violation	Violation of inclusion/exclusion criteria. Or missing documentation of any of the inclusion/exclusion criteria at time of enrollment.
Procedural deviation	Deviation to any study procedures.
Mis-randomization	Misclassification of subject's sex at randomization. Or incorrect product administered according to randomized sequence.
Use of TNP not allowed	Use of any nicotine or tobacco–containing product other than the assigned product during the exposure period, or use of any nicotine tobacco-containing product during at least 23 hours of abstinence from any nicotine/tobacco containing products (nicotine wash-out).

5. PRODUCT DESCRIPTIONS

5.1 Test Products

Test product will be the THS induction device with regular and menthol sticks, provided by the Sponsor. The following two stick variants will be investigated:

Name in the study (sticks)	Flavor
P1R stick	Regular
P1M stick	Menthol

The test products will be listed as:

Name in the study (test products)	Abbreviated name (test products)
THS regular stick (P1R)	P1R
THS menthol stick (P1M)	P1M

5.2 Comparator Product

The subjects will bring their own supply of commercially available single brand CIG for the study duration.

The comparator product will be listed as:

Name in the study (comparator product)	Abbreviated name (comparator product)
Combustible cigarette	CIG

All subjects eligible at Screening visit and invited for Baseline visit Day -1 will be asked to purchase their usual brand of CIG and to provide it to the site personnel at their admission on Baseline (Day -1). Every subject will bring an unopened pack of CIG which will be kept in secured storage room at site with access limited to authorized personnel.

6. PHARMACOKINETIC ANALYSIS

6.1 Collection Schedule for Plasma Nicotine

Collection schedule is described in Table 6.1.

Table 6.1 Plasma Nicotine Samples Collection Schedule

Day 1 (14 blood samples)	Prior to the start of product use (T_B0) ≤5 min (±2 min) prior to T0. In relation to T0 from Day 1: T_B1 after 4 minute ± 30 seconds, T_B2 after 6 minutes ± 1 minute, T_B3 after 8 minutes ± 1 minute, T_B4 after 10 minutes ± 1 minute, T_B5 after 12 minutes ± 1 minute, T_B6 after 15 minutes ± 2 minutes, T_B7 after 30 minutes ± 5 minutes, T_B8 after 1 hour ± 5 minutes, T_B9 after 2 hours ± 5 minutes, T_B10 after 4 hours ± 5 minute, T_B11 after 10 hours ± 5 minutes, T_B12 after 14 hours ± 5 minutes, T_B13 after 24 hours ± 10 minutes
Day 2 (13 blood samples)	Same time points from T_B1 to T_B13. T_B0 for Day 2 will be the same sample taken as T_B13 on Day 1.
Day 3 (11 blood samples)	Same time points from T_B1 to T_B11 and no samples for T_B12, T_B13. T_B0 for Day 3 will be the same sample taken as T_B13 on Day 2.

6.2 Plasma Nicotine Concentrations

Analytical Laboratory

Samples will be analyzed for nicotine in plasma using a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) detection analytical method with the appropriate quality controls in accordance with the Food and Drug Administration (FDA)

Guidance for Industry: Bioanalytical Method Validation (May, 2001) and in accordance with FDA Good Laboratory Practice regulations (Title 21 CFR Part 58) at [redacted] Bioanalytical Services Lincoln, Nebraska.

6.3 Plasma Nicotine Pharmacokinetic Parameters

Nicotine PK endpoints will be derived from measured plasma nicotine concentration-time data. Nicotine PK parameters will be derived using a non-compartmental analysis (NCA) technique using appropriate and validated PK software (e.g., Phoenix WinNonlin version 8.3.4 or higher).

For values above the upper limit of quantification (ULOQ), the ULOQ will be used for calculation and reporting in summary tables. For nicotine concentrations below the LLOQ (BLQ) for the calculation of descriptive statistics of observed plasma nicotine concentrations: In general, BLQ values before T0 will be imputed by LLOQ/2.

Plasma concentrations as determined at the collection times described in Section 6.1 will be used for the calculation of the plasma nicotine PK parameters.

BLQ values after the last quantifiable value are not included in the analysis (e.g., for the calculation of AUC).

Any BLQ value (after T0 and before the last quantifiable value) would need to be queried* and, if confirmed, it will be imputed by LLOQ/2.

*The query will be triggered at the latest by [redacted] data QC, and [redacted] will query the bioanalytical laboratory. The information on the value queried and a summarized response from the bioanalytical laboratory will be part of the SDTM data (e.g. in the CO domain).

The number and percent of values below LLOQ or above ULOQ will be presented in each summary table. If 50% or more data are below LLOQ or above ULOQ, only the number and percent of values below LLOQ or above ULOQ will be reported in the summaries, together with minimum (= LLOQ/2) and maximum (= ULOQ) of the observed values.

In particular, the following PK parameters will be derived from measured nicotine concentration-time data following IP use:

Cmax	Maximum nicotine plasma concentration. Cmax will be reported as long as there is at least one quantifiable concentration post T0.
Tmax	Time to maximum nicotine plasma concentration Cmax.
AUC0-24	Area under the curve of nicotine plasma concentration-time computed from T0 to T=24 hours [AUC0-24h].
AUC0-Tmax	Area under the curve of nicotine plasma concentration-time computed from T0 to the subject-specific time of maximum nicotine concentration [AUC0-Tmax].

All AUC parameters will be calculated using linear trapezoidal with linear interpolation method.

For PK analyses, baseline (pre-product use concentration) will be defined as the last assessment prior to T0 (5 minutes prior to T0) for each study day of exposure. PK parameters will not be calculated for subjects with less than 3 consecutive post-product use time points with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables and individual concentration-time figures only and excluded from the summary and statistical analysis.

6.4 Data Summarization and Presentation

SAS software (version 9.4, Cary, North Carolina) will be used for all data presentation and summarization including statistical analyses, summary tables, graphs, and data listings.

All data will be presented in listings, ordered by subject, study visit, IP, and time point, unless otherwise specified.

PK data will be summarized for the PK population. In addition, PK data will also be summarized for the randomized population if there is at least a difference of 1 subject between the populations.

The 95% confidence interval (CI) of the arithmetic mean, median, first and third quartiles, minimum, maximum; for log-normal data, the geometric mean, geometric coefficient of variation (CV), and 95% CI of the geometric mean will be presented instead of arithmetic mean, SD, and 95% CI of the arithmetic mean, respectively.

For log normally distributed endpoints (Cmax, AUC0-24h and AUC0-Tmax), geometric mean, geometric CV, and confidence interval will be presented additionally.

Measured plasma nicotine concentrations and derived PK parameters will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data (Missing, n (%)), arithmetic mean (Mean), arithmetic standard deviation (SD), 95% confidence interval (95%CI), minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Summaries will be further stratified by Sex.

For log normally distributed endpoints (Cmax, AUC0-24h and AUC0-Tmax), geometric mean (Geo. Mean), 95% geometric confidence interval (Geo. 95% CI) and geometric CV (Geo. CV%) will be presented additionally.

For observed plasma nicotine concentrations, the number and percent of values below LLOQ (BLQ, n(%)) or above ULOQ (ALQ, n(%)) will be presented in each summary table.

Ordinal categorical data (e.g., Tmax) will be summarized by number of subjects (n), number and percent of subjects with missing data, median, first and third quartiles, and minimum and maximum.

All PK analyses and summaries will be performed by product.

The analytical data will be presented in the tables/listings to the same precision as received from the analytical laboratory.

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. Missing PK data will be treated as missing and no data imputation will be conducted.

Mean and individual plasma nicotine concentrations will be presented graphically (linear and semi-log plots; linear plots will be presented with and without SD).

6.5 Statistical Analysis of Pharmacokinetic Parameters

6.5.1 Main Analysis

A mixed model analysis of variance (ANOVA) will be conducted on Cmax, AUC0-24h, and AUC0-Tmax endpoints in the natural logarithmic scale.

The model will include terms for sequence, period, product as fixed effects and subject as a categorical random effect modeling the within subject correlations.

The ANOVA analysis could be performed using the following SAS code:

```
PROC MIXED data=< > method=REML;
class subject sequence period product;
model log(parameter) = sequence period product/ddfm=KR;
repeated product / subject=subject type=csh;
lsmeans product / pdiff=control("CIG") cl alpha=0.05;
RUN;
```

The results of this analysis for each of are presented in terms of geometric least square ratios and 95% confidence intervals for each THS / CIG ratio.

This approach is consistent with the guidelines in the European Medicines Agency's guidelines for bioequivalence investigations and FDA's Center for Drug Evaluation and Research.

The analysis of Tmax will be performed by conducting a Wilcoxon signed rank test and calculating the median Tmax for each product along with the Hodges-Lehmann estimate of the median difference between products, and the related 95% CI.

This analysis could be performed using the following SAS code:

```
PROC NPAR1WAY hl(refclass=<>) alpha=.05 data=<> hl;
class TRT;
var AVAL;
ods output HodgesLehmann=HodgesLehmann;
RUN;
```

6.5.2 Sensitivity Analyses

In case of any uncorrected nicotine concentration at T_0 [uC_0] greater than 5% of their uncorrected maximum value, a sensitivity analysis of the PK endpoints will be performed similarly to the main analysis, whereby data of these subjects for this specific study day will be excluded from the analysis.

6.5.3 Supplementary Analysis

No supplementary analysis is foreseen.

6.6 Preliminary Data and Interim Analysis

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

7. PHARMACODYNAMIC EFFECTS (SUBJECTIVE EFFECTS)

7.1 Data Collection

On Day 1 to Day 3, cigarette craving, product liking, and intention to use the product again will be assessed using a VAS (a 100 mm unipolar scale going from “no craving” to “strong craving” for VAS Craving; a 100 mm bipolar scale going from “strong disliking” to “strong liking” for VAS Liking; and a 100 mm bipolar scale going from “very unlikely” to “very likely” for VAS Intention to Use Again) at the following time points in relation to T0 with a time window as indicated in brackets:

Prior to T0 (for VAS Craving assessment)

- Tv0: within 15 minutes prior to T0

After T0 (for VAS Craving assessment)

- Tv1 after 4 minutes (± 2 minutes)
- Tv2 after 10 minutes (± 2 minutes)
- Tv3 after 15 minutes (± 2 minutes)
- Tv4 after 30 minutes (± 2 minutes)
- Tv5 after 10 hours (± 5 minutes)

After T0 (for VAS Liking and VAS Intention to Use Again assessments)

- Tv3 after 15 minutes (± 1 minute)

7.2 Data Summarization

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% CI of mean) for VAS Craving assessment, VAS Liking assessment, and VAS

Intention to Use Again assessment will be provided by IP and assessment time point, as applicable. Change from baseline (pre-product use) for VAS Craving score will be summarized by IP and assessment time point. Individual responses will be listed. Summaries will be further stratified by sex.

PD data will be summarized for the PK population. In addition, PD data will also be summarized for the randomized population if there is at least a difference of 1 subject between the populations.

8. SAFETY

All relevant case report form (CRF) 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 product use in the respective period unless otherwise stated. Summaries for post-baseline time points will not include rechecks, unscheduled, or early termination measurements.

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

8.1 Subject Disposition

Subjects will be summarized by number of subjects screened, enrolled, enrolled and exposed to P1 product, randomized, completed, and discontinued the study with discontinuation reasons.

8.2 Protocol Deviations

Protocol deviations are captured by the clinical site and provided in the CSR in a similar format to that provided by the clinical site. Protocol deviations are not edited or processed in SAS®.

8.3 Demographics

Descriptive statistics will be calculated overall for continuous variables (age, weight, height, and body mass index) and further stratified by sex.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) overall and further stratified by sex.

Demographic information and baseline characteristics (weight, height, and body mass index [BMI]) will be summarized for the safety and PK population. This summary will also be performed for the randomized population if there is at least a difference of 1 subject between the populations.

8.4 Tobacco/Nicotine-Containing Product Use History Questionnaire

At the Screening Visit, subjects will be asked questions about their tobacco-and/or nicotine-containing product (TNP) use history. The questions will capture frequency and quantity of TNP use over the past 4 weeks, and number of continuous years of cigarette smoking.

Descriptive statistics will be calculated for continuous variables overall and further stratified by sex.

Frequency counts and percentage will be provided for categorical variables overall and further stratified by sex.

8.5 Usual Brand Cigarettes Documentation

Subject's usual brand of cigarettes will be documented and frequency counts will be provided for categorical variables (substance, brand, brand style, flavor, and cigarette length) overall and further stratified by sex. Descriptive statistics will be presented for amount of use overall and further stratified by sex.

8.6 Fagerström Test for Nicotine Dependence (FTND)

Potential nicotine dependence will be assessed at the Screening Visit using the FTND in its revised version as updated in 2012 (Fagerström, K.O., 1978, Heatherton, T.F., et al., 1991). The questionnaire consists of six questions, which have to be answered by the subject himself/herself. The total score obtained on the test permit the classification of nicotine dependence into three levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points) (Fagerström, K., et al., 2012).

Descriptive statistics will be calculated for FTND score. In addition, frequency counts will be provided for nicotine dependence levels (mild, moderate, and severe) overall and further stratified by sex.

8.7 Medical History

All Medical History and Concomitant Disease will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 25.1 and listed by subject.

8.8 Adverse Events

All AEs occurring during this clinical trial will be coded using MedDRA®, Version 25.1.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, product, severity, relationship to study product, and action; however, only product use-emergent AEs (PUEAEs) will be summarized. Adverse events after ICF and prior to the first product use on Day 1 and occurred during SFU period (after discharge from CRU to SFU visit) will be summarized separately under admission/SFU period.

A PUEAE is defined as an AE that is starting or worsening at the time of or after first study product administration. An AE that occurs during the washout period between study products is considered study product use emergent to the last study product given.

If the onset time of an AE is missing and the onset date is the same as the product administration date, the AE will be considered product use-emergent to the prior and current product. If the onset time of an AE is missing and the onset date does not fall on a product administration date, the AE will be considered product use-emergent for the last product administered. If the onset date of an AE is missing, the AE will be considered product use-emergent and attributed to each product on the study, unless the onset date is known to have occurred within or between specific product periods.

The number and percentage of subjects with AEs, SAEs will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to discontinuation, AEs leading to death, AEs by relatedness to product exposure, AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events.

SAEs, if present, will also be listed. Applicable narratives will be included in the CSR.

8.9 Clinical Laboratory Tests (Serum Chemistry, Hematology, and Urinalysis)

Clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) will be performed at Screening, Admission (Day -1), and at the time of discharge (Day 3) or as early termination assessments, as applicable.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a computer clinically significant (CS) range. If the value falls within the computer CS range, it will be noted as “N” for not clinically significant. If the value fails (i.e., fall outside of the CS range) the computer CS range, it will be flagged with a

"Y" which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. To distinguish the PI flag from the computer CS range flags, the PI flags of "N" and "Y" will be presented as "-" and "+", respectively, in the data listing. Additionally, a derived flag based on a search of the PI comments for a comment of "CS" or "Clinically Significant" will be used. The derived flag will be populated with "+" if the positive clinically significant determination is found in the comments for cases when the PI flag is populated with a "^" or a "R".

Out-of-range values and corresponding recheck results will be listed. CTCAE laboratory grading (version 5.0) will be included as well. Other lab results within this panel and time point will also be listed for this subject. Results that are indicated as CS by the PI will be listed in the table.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by time point (baseline and discharge). Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected on Admission (Day -1). Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

8.10 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate) will be measured at the Screening Visit, on Admission (Day -1), Preuse on Period 1, Period 2, and Period 3, and Discharge (Period 3) or as early termination assessments, as applicable. All parameters will be recorded in supine position after the subject has rested for at least 5 minutes. Subjects should have abstained from using any TNPs for at least 15 minutes prior to Vital signs assessment.

The Investigator will define vital sign ranges to determine normal or abnormal results. For those results outside of the normal range, the Investigator will determine appropriate follow up including reporting of any AEs.

Descriptive statistics will be reported for vital signs measurements (blood pressure, pulse, respiration, and temperature) by time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected on prior to T0 on Day 1. Post product use unscheduled events or rechecks

will not be included in summaries. Similarly, early termination results will not be included in summaries.

8.11 Electrocardiogram

An ECG will be recorded at Screening, Admission (Day -1), and at discharge or at early termination. The ECG testing will be performed as per the investigational site standard practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval, corrected by the ECG device according to Fridericia's formula [QTcF]. Each ECG will be assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant.

Descriptive statistics will be presented for each ECG parameter by time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected at Admission (Day -1). Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

8.12 Prior and Concomitant Medications and Concomitant Procedures

All prior and concomitant medications will be listed by subject and product using Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization Drug Dictionary) Version 01 Sep 2022 b3. Prior and concomitant medications concomitant procedures recorded during the study will be listed by subject.

8.13 Physical Examination

A physical examination will be conducted at the Screening Visit. All data found in the CRF will be listed. Physical examination will be assessed as normal, abnormal – clinically not significant, or abnormal – clinically significant.

8.14 Spirometry

Spirometry without bronchodilator will be performed at the Screening Visit, Day -1, and at Discharge or early termination in accordance with the 2019 guideline update of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry (Graham, B.L., et al., 2019). Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set.

Assessed parameters will include: FEV1, FEV1% predicted, FVC, FVC% predicted, and FEV1/FVC.

Every Spirometry assessment has to be classified as normal, abnormal – clinically not significant, or abnormal – clinically significant.

Descriptive statistics will be presented for each spirometry parameter by time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected at Day -1. Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

8.15 Product Events

All product events occurring during this clinical trial will be collected and 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.

10. REFERENCES

Committee for Medicinal Products for Human Use (CHMP) and European Medicines Agency (EMA), *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)*. 2010.

Fagerström, K.O., 1978
Fagerström, K.O., Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav, 1978. 3(3-4): p. 235-41.

Fagerström, K., et al., 2012
Fagerström, K., et al., The Fagerström Test for Nicotine Dependence as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data. Nicotine and Tobacco Research, 2012. 14(12): p. 1467-73.

FDA (Food and Drug Administration), *Guidance for industry – Statistical approaches to establishing bioequivalence.* 2001. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf (Accessed on 24 April 2014)

Heatherton, T.F., et al., 1991
Heatherton, T.F., et al., The Fagerström test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict, 1991. 86(9): p. 1119-27.

Graham, B.L. et. al. 2019
Graham, B.L. et. al., Standardization of Spirometry 2019 Update. Am J Respir Crit Care Med Vol 200, Iss 8, pp e70–e88, Oct 15, 2019.

11. 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, as appropriate.

In-text tables and figures will be generated as RTF and all other tables and listings will be generated as SAS® LST format and converted to MS Word for inclusion in the CSR. In compliance [redacted] SOP/PG, SAS® outputs will not be manually edited.

11.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Number	Title	Shell
Table 10-1	Disposition Summary (Safety Population)	IDS

Section 11:

Number	Title	Shell
Table 11-1	Summary of Demographics and Baseline Characteristics (Safety Population)	IDEM
Table 11-2	Summary of Plasma Nicotine PK Parameters of THS and CIG (PK Population)	ITPPar1
Table 11-3	Statistical Comparisons of Plasma Nicotine PK Parameters for THS and CIG (PK Population)	ITPStat1
Table 11-4	Statistical Comparisons of Plasma Nicotine PK Parameter Tmax for THS and CIG (PK Population)	ITPStat2
Table 11-5	Summary of VAS Craving Assessment (PK Population)	ITPDSum1
Table 11-6	Summary of VAS Liking Assessment (PK Population)	ITPDSum2
Table 11-7	Summary of VAS Intention to Use Again Assessment (PK Population)	ITPDSum2
Figure 11-1	Arithmetic Mean Plasma Nicotine Concentration Versus Time Profiles Following Administration of THS and CIG (Linear Scale) (PK Population)	PFPConc2

Section 12:

Number	Title	Shell
Table 12-1	Overall Product Use Emergent Adverse Events (Safety Population)	IAEO
Table 12-2	Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population)	IAES

11.2 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

Note: Demographic TFLs may also include PK population. If so, the applicable titles will read: "Safety and PK Populations".

Number	Title	Shell
Table 14.1.1	Disposition Summary (Safety Population)	CDS
Table 14.1.2	Subject Product Use Status and Study Disposition (Safety Population)	SDS
Table 14.1.3	Demographic Summary (Safety Population)	CDEM
Table 14.1.4	Tobacco/Nicotine-Containing Product Use History Summary (Safety Population)	CUB
Table 14.1.5	Usual Brand Cigarettes Summary (Safety Population)	CSU
Table 14.1.6	Fagerstrom Test for Nicotine Dependence Summary (Safety Population)	CFT

14.2 Pharmacokinetic/Pharmacodynamic Data Summary Tables and Figures

Note: PK and PD TFLs may also include Randomized population. If so, the applicable titles will read: "PK and Randomized Populations".

14.2.1 Plasma Nicotine Tables

Number	Title	Shell
Table 14.2.1.1	Plasma Nicotine Concentrations (ng/mL) Following THS Regular stick (P1R) (PK Population)	CPCONC1

Number	Title	Shell
Table 14.2.1.2	Plasma Nicotine Concentrations (ng/mL) Following THS Menthol stick (P1M) (PK Population)	CPCONC1
Table 14.2.1.3	Plasma Nicotine Concentrations (ng/mL) Following Combustible Cigarette (CIG) (PK Population)	CPCONC1
Table 14.2.1.4	Plasma Nicotine Pharmacokinetic Parameters Following THS Regular stick (P1R) (PK Population)	CPPAR1
Table 14.2.1.5	Plasma Nicotine Pharmacokinetic Parameters Following THS Menthol stick (P1M) (PK Population)	CPPAR1
Table 14.2.1.6	Plasma Nicotine Pharmacokinetic Parameters Following Combustible Cigarette (CIG) (PK Population)	CPPAR1
Table 14.2.1.7	Statistical Comparison of Plasma Nicotine Pharmacokinetic Parameters: THS Versus CIG (PK Population)	CPStat1
Table 14.2.1.8	Nonparametric Statistical Comparison of Plasma Nicotine Tmax: THS Versus CIG (PK Population)	CPStat1

14.2.2 Plasma Nicotine Figures

Number	Title	Shell
Figure 14.2.2.1	Arithmetic Mean (SD) Plasma Nicotine Concentration Versus Time Profiles Following Administration of THS and CIG (Linear Scale) (PK Population)	PFPConc1
Figure 14.2.2.2	Arithmetic Mean Plasma Nicotine Concentration Versus Time Profiles Following Administration of THS and CIG (Linear Scale) (PK Population)	PFPConc2
Figure 14.2.2.3	Arithmetic Mean Plasma Nicotine Concentration Versus Time Profiles Following Administration of THS and CIG (Semi-Log Scale) (PK Population)	PFPConc3

14.2.3 Subjective Effects and Related Behavioral Assessment Tables

Number	Title	Shell
Table 14.2.3.1	Summary of VAS Craving Assessment by Study Product and Time Point (PK Population)	CPD1
Table 14.2.3.2	Summary of VAS Liking Assessment by Study Product (PK Population)	CPD1

Number	Title	Shell
Table 14.2.3.3	Summary of VAS Intent to Use Again Assessment by Study Product and Time Point (PK Population)	CPD1

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Number	Title	Shell
Table 14.3.1.1	Overall Product Use Emergent Adverse Event Frequency by Study Product – Number of Subjects Reporting the Event (% of Subjects Used IP) (Safety Population)	CAEO
Table 14.3.1.2	Product Use Emergent Adverse Event Frequency by Study Product – Number of Subjects Reporting the Event (% of Subjects Used Study Product) (Safety Population)	CAES
Table 14.3.1.3	Product Use Emergent Serious Adverse Event Frequency by Study Product – Number of Subjects Reporting the Event (% of Subjects Used Study Product) (Safety Population)	CAES
Table 14.3.1.4	Product Use Emergent Adverse Event Frequency by Study Product – Number of Adverse Events (% of Total Adverse Events) (Safety Population)	CAEE
Table 14.3.1.5	Product Use Emergent Serious Adverse Event Frequency by Study Product – Number of Adverse Events (% of Total Adverse Events) (Safety Population)	CAEE
Table 14.3.1.6	Product Use Emergent Adverse Event Frequency by Study Product, Severity, and Relationship to Study Product – Number of Adverse Events (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 – Serum 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)	
Table 14.3.4.4	Clinically Significant Values and Recheck Results (Safety Population)	CLBS

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Number	Title	Shell
Table 14.3.5.1	Clinical Laboratory Summary and Change From Baseline – Serum Chemistry (Safety Population)	CLBD
Table 14.3.5.2	Clinical Laboratory Shift From Baseline – Serum Chemistry (Safety Population)	CLBS
Table 14.3.5.3	Clinical Laboratory Summary and Change From Baseline – Hematology (Safety Population)	CLBD
Table 14.3.5.4	Clinical Laboratory Shift From Baseline – Hematology (Safety Population)	CLBS
Table 14.3.5.5	Clinical Laboratory Summary and Change From Baseline – Urinalysis (Safety Population)	CLBD
Table 14.3.5.6	Clinical Laboratory Shift From Baseline – Urinalysis (Safety Population)	CLBS
Table 14.3.5.7	Vital Sign Summary and Change From Baseline (Safety Population)	CVS
Table 14.3.5.8	12-Lead Electrocardiogram Summary and Change From Baseline (Safety Population)	CEG
Table 14.3.5.9	Spirometry Summary and Change From Baseline (Safety Population)	CSP

11.3 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 CRF (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 – Pharmacokinetics

16.1.10 Clinical Laboratory Reference Ranges

Number	Title
Appendix 16.1.10.1	Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Number	Title
Appendix 16.2.1.1	Subject Disposition (Safety Population)
Appendix 16.2.1.2	Subject Disposition (Screen Failures)

16.2.2 Protocol Deviations

Number	Title
Appendix 16.2.2.1	Protocol Deviations

16.2.3 Subjects Excluded From the Pharmacokinetic/Pharmacodynamic Analysis

Number	Title
Appendix 16.2.3.1	Subjects Excluded From the Pharmacokinetic/Pharmacodynamic Analysis

Note: Appendices 16.2.2.1 and 16.2.3.1 are generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Number	Title
Appendix 16.2.4.1	Demographics (Safety Population)
Appendix 16.2.4.2	Demographics (Screen Failure)
Appendix 16.2.4.3	Informed Consent (Safety Population)
Appendix 16.2.4.4	Informed Consent (Screen Failure)
Appendix 16.2.4.5	Physical Examination (I of II) (Safety Population)
Appendix 16.2.4.6	Physical Examination (II of II) (Safety Population)
Appendix 16.2.4.7	Physical Examination Descriptions (Safety Population)
Appendix 16.2.4.8	Medical History (Safety Population)
Appendix 16.2.4.9	Tobacco/Nicotine-Containing Product Use History (Safety Population)
Appendix 16.2.4.10	Usual Brand Cigarettes Documentation (Safety Population)
Appendix 16.2.4.11	Fagerstrom Test for Nicotine Dependence (Safety Population)

16.2.5 Compliance and/or Concentration Data

Number	Title
Appendix 16.2.5.1	Subject Enrollment (Safety Population)
Appendix 16.2.5.2	Subject Eligibility (Safety Population)
Appendix 16.2.5.3	Subject Eligibility (Screen Failure)
Appendix 16.2.5.4	Randomization (Safety Population)
Appendix 16.2.5.5	Investigational Product Administration (Safety Population)
Appendix 16.2.5.6	Prior and Concomitant Medications (Safety Population)
Appendix 16.2.5.7	Plasma Nicotine Pharmacokinetic Blood Draw Times and Concentration Data (Safety Population)

16.2.6 Individual Pharmacokinetic/Pharmacodynamic Response Data

Number	Title	Shell
Appendix 16.2.6.1	Individual Plasma Nicotine Concentrations Versus Time for <Subject #> (Linear and Semi-Log Scale)	PFPConc5
Appendix 16.2.6.2	VAS Craving Assessment (Safety Population)	
Appendix 16.2.6.3	VAS Liking Assessment (Safety Population)	
Appendix 16.2.6.4	Intention to Use Again (Safety Population)	

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	Product Events (Safety Population)

16.2.8 Clinical Laboratory Reports

Number	Title
Appendix 16.2.8.1	Clinical Laboratory Report - Serum 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	Clinical Laboratory Report - Urine Drug Screening (Safety Population)
Appendix 16.2.8.5	Clinical Laboratory Report - Virology (Safety Population)
Appendix 16.2.8.6	Alcohol Breath Test (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)

12. 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 in-text tables will be presented in Times New Roman font size 9 and post-text tables will be presented in Courier New font size 9. In-text tables and figures will be generated as RTF and all other tables and listings will be generated as SAS® LST format and converted to MS Word for inclusion in the CSR. In compliance [redacted] SOP/PG, SAS® outputs will not be manually edited.

12.1 In-text Summary Tables Shells

In-text Shell IDS will be in the following RFT format:

Table IDS Disposition Summary (Safety Population)

Category	Overall
Screened	XXX
Enrolled	XX
Enrolled and Exposure to P1 Product	XX
Randomized	XX (100%)
Completed Study	XX (XX%)
Discontinued From Study	XX (XX%)
<Reason>	XX (XX%)
Source: Table 14.1.1 Program: /CAXXXXX/sas_prg/stsas/intext/t_disp.sas DDMMMYYYY HH:MM	

In-text Shell IDM will be in the following RFT format:

Table IDEM Summary of Demographics and Baseline Characteristics (Safety Population)

Trait	Category/Statistic	Overall
Sex	Female	XX (XX%)
	Male	XX (XX%)
Race	Asian	XX (XX%)
	Black or African American	XX (XX%)
	White	XX (XX%)
Ethnicity	Hispanic or Latino	XX (XX%)
	Not Hispanic or Latino	XX (XX%)
Age (yr)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Body Mass Index (kg/m²)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Height (cm)	N	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Weight (kg)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Descriptive statistics for body mass index, height, and weight are calculated using Screening measurements. Source: Table 14.1.3 Program: /CAXXXXX/sas_prg/stsas/intext/t_dem.sas DDMMMYYYY HH:MM		

Programmer Note: If there is at least a difference of 1 subject between the safety, Randomized, and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.

In-text shell ITPPar1 will be in the following RFT format:

Table ITPPar1

Summary of Plasma Nicotine PK Parameters of THS and CIG (PK Population)

Pharmacokinetic Parameters	THS regular stick (P1R)	THS menthol stick (P1M)	Combustible Cigarette (CIG)
Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param4 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Product <X>: <Label for Second Product> Product <Y>: <Label for First Product > Product <Z>: <Label for Third Product > AUCs and Cmax values are presented as geometric mean and geometric CV%. Tmax values are presented as median (min, max). Source: Tables 14.2.1.4 through 14.2.1.6			

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order and with following units: Cmax <ng/mL>, Tmax <min>, AUC0-24 <ng*min/mL>, and AUC0-Tmax <ng*min/mL>;
- n will be presented as an integer (with no decimal);
- Summary statistics will be presented with same precision as defined in post-text shells

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Programmer Note: If there is at least a difference of 1 subject between the Randomized and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.

In-text shell ITPStat1 will be in the following RFT format:

Table ITPStat1

Statistical Comparisons of Plasma Nicotine PK Parameters for THS and CIG (PK Population)

Parameter	Product <X> (Test)		Product <Y> (Comparator)		GMR (%)	95% Confidence Interval	Intra subject CV%
	Geometric LSMs	n	Geometric LSMs	n			
param1 (units)	XXX.X	XX	XXX.X	XX	XX.XX	XX.XX - XX.XX	X.XX
param2 (units)	XXX.X	XX	XXX.X	XX	XX.XX	XX.XX - XX.XX	X.XX
param3 (units)	XXX.X	XX	XXX.X	XX	XX.XX	XX.XX - XX.XX	X.XX

Product <X>: <Label for Test Product>
Product <Y>: <Label for Comparator Product >
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/comparator)
Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.1.7

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order and with following units: Cmax (ng/mL), AUC0-24 <ng*min/mL>, and AUC0-Tmax <ng*min/mL>;
- n will be presented as an integer (with no decimal);
- All statistics will be presented with same precision as defined in post-text shells
- The comparisons will be: P1R vs CIG and P1M vs CIG, where P1R = THS regular stick; P1M = THS menthol stick; and CIG = Combustible cigarette.
- Add column identifying the comparisons.

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Programming notes: The following comparisons will be included in the table: P1R versus CIG and P1M versus CIG.
If there is at least a difference of 1 subject between the Randomized and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.

In-text shell ITPStat2 will be in the following RFT format:

Table ITPStat2

Statistical Comparisons of Plasma Nicotine Pharmacokinetic Parameter Tmax for THS and CIG (PK Population)

Comparison	Parameter	Difference <X> - <Y>		
		Median	95% Confidence Interval	p-value
P1R vs CIG	Tmax	X.XX	X.XX-X.XX	X.XXXX
P1M vs CIG	Tmax	X.XX	X.XX-X.XX	X.XXXX

P1R: < >
P1M: < >
CIG: < >

The difference between products (product effect) and the 95% confidence interval for the difference was calculated using Hodges-Lehmann estimator.

Source: Table 14.2.1.8

Notes for Generating the Actual Table:

Presentation of Data:
- Median difference will be presented to 2 decimals or 3 significant figures
- 95% CI will be presented to 4 decimals
- p-value will be presented to 4 decimals

Programming notes: The following comparisons will be included in the table: P1R versus CIG and P1M versus CIG.
If there is at least a difference of 1 subject between the Randomized and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.

In-text Shell ITPDSum1 will be in the following RFT format:

Table ITPDSum1 Summary of VAS Craving Assessment (PK Population)

Time Point	THS regular stick (P1R)	THS menthol stick (P1M)	Combustible Cigarette (CIG)
Tv0: Within 15 minutes prior to T0	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Tv1 after 4 minutes	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Tv2 after 10 minutes	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Tv3 after 15 minutes	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Tv4 after 30 minutes	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Tv5 after 10 hours	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Values are presented as arithmetic mean (± SD). Source: Tables <XXXX> and <YYYY>			

Programmer Note: If there is at least a difference of 1 subject between the Randomized and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.

In-text Shell ITPDSum2 will be in the following RFT format:

Table ITPDSum2 Summary of VAS Liking Assessment (PK Population)

Time Point	THS regular stick (P1R)	THS menthol stick (P1M)	Combustible cigarette (CIG)
Tv3 after 15 minutes	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Values are presented as arithmetic mean (± SD). Source: Tables <XXXX> and <YYYY>			

Programmer Note: If there is at least a difference of 1 subject between the Randomized and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.

In-text Shell IAEO will be in the following RFT format:

Table IAEO Overall Product Use Emergent Adverse Events (Safety Population)

		Product Administration				
Adverse Event	**Admission (N=X)**	**P1R (N = X)**	**P1M (N-X)**	**CIG (N = X)**	**Overall (N = X)**	**SFU (N = X)**
Number of Subjects With PUEAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Number of Subjects With SAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Number of Subjects With IP Events	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Number of Subjects With AEs Leading to Discontinuation	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Number of Subjects With AEs Leading to Death	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Number of Subjects With AEs Related to IP	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

P1R: THS regular stick
P1M: THS menthol stick
CIG: Combustible cigarette
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.

PUEAEs = Product use-emergent adverse events; SAEs = Serious adverse events; IP = Investigational product
Admission = after ICF and prior to the product test on Day 1
SFU = after discharge from CRU to safety follow-up visit

Source: Table 14.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

In-text Shell IAES will be in the following RFT format:

Table IAES Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population)

		Product				
Adverse Event	**Admission (N=X)**	**P1R (N = X)**	**P1M (N-X)**	**CIG (N = X)**	**Overall (N = X)**	**SFU (N = X)**
Number of Subjects With PUEAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Number of Subjects Without PUEAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Eye disorders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Visual blurred	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Gastrointestinal disorders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Dyspepsia	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Nausea	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Musculoskeletal and connective tissue disorders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Back pain	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Muscle cramps	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Musculoskeletal pain	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Nervous system disorders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Headache	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Reproductive system and breast disorders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Vaginal discharge	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Respiratory, thoracic and mediastinal disorders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Epistaxis	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Skin and subcutaneous tissue disorders	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Sweating increased	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

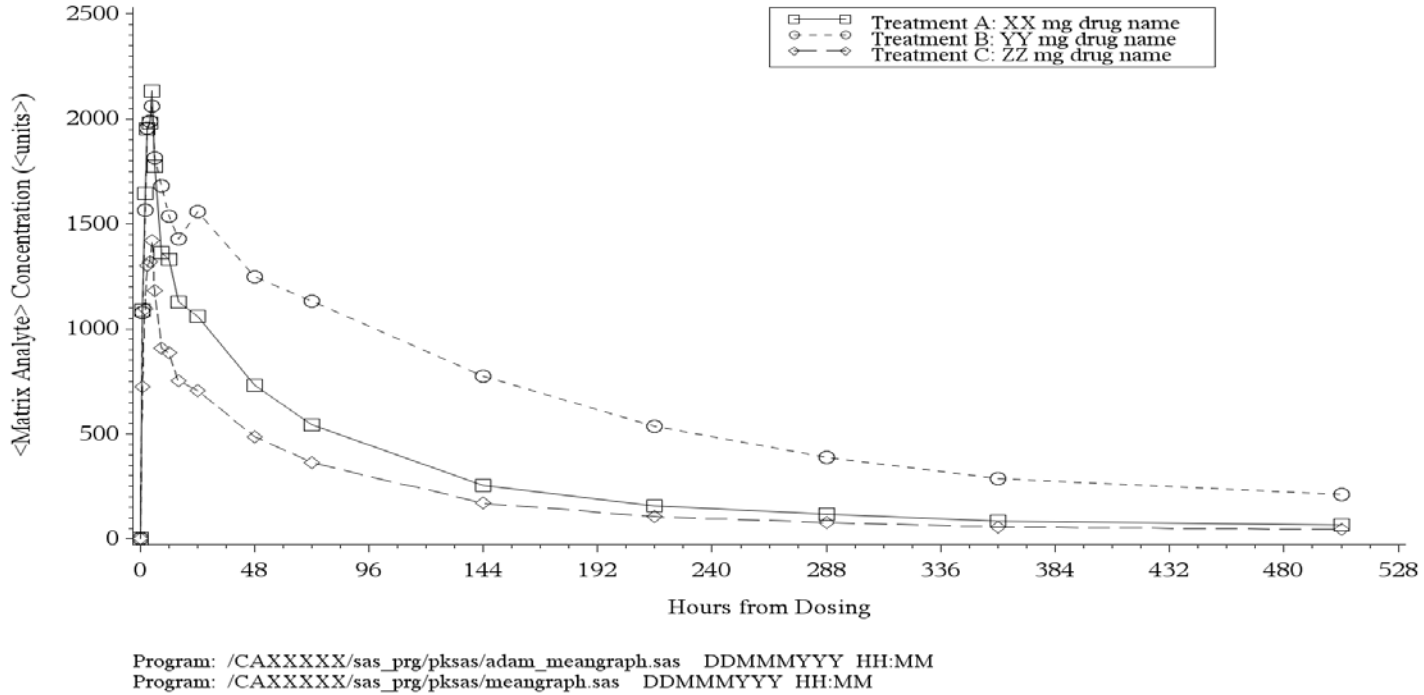
P1R: THS regular stick
P1M: THS menthol stick
CIG: Combustible cigarette
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.
Adverse events are classified according to MedDRA Version 25.1.
PUEAEs = Product use-emergent adverse events
Admission = after ICF and prior to the product test on Day 1
SFU = after discharge from CRU to safety follow-up visit

Source: Table 14.3.1.2
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

12.2 Figures Shells

Figures PFPConc2 (both in-text and post-text) will be in the following RFT format:

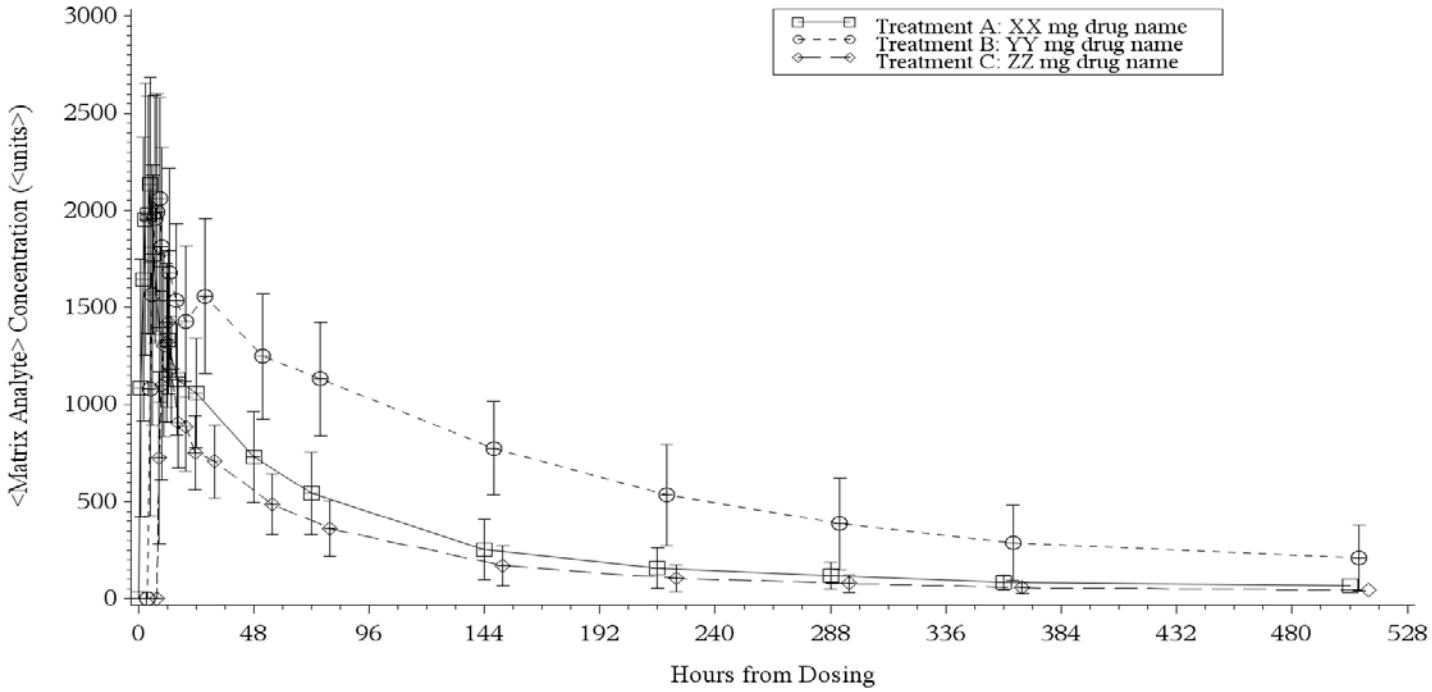
Figure Mean Plasma Nicotine Concentrations Versus Time (Linear Scale) (PK Population)



Programming note : the legend will present the 3 products ‘Product X: Product Description’
The x-axis title will be: ‘Time From Start of Product Use (min)’.

Figure PFPConc1 will be in the following RFT format:

Figure Mean (SD) Plasma Nicotine Concentrations Versus Time (Linear Scale) (PK Population)

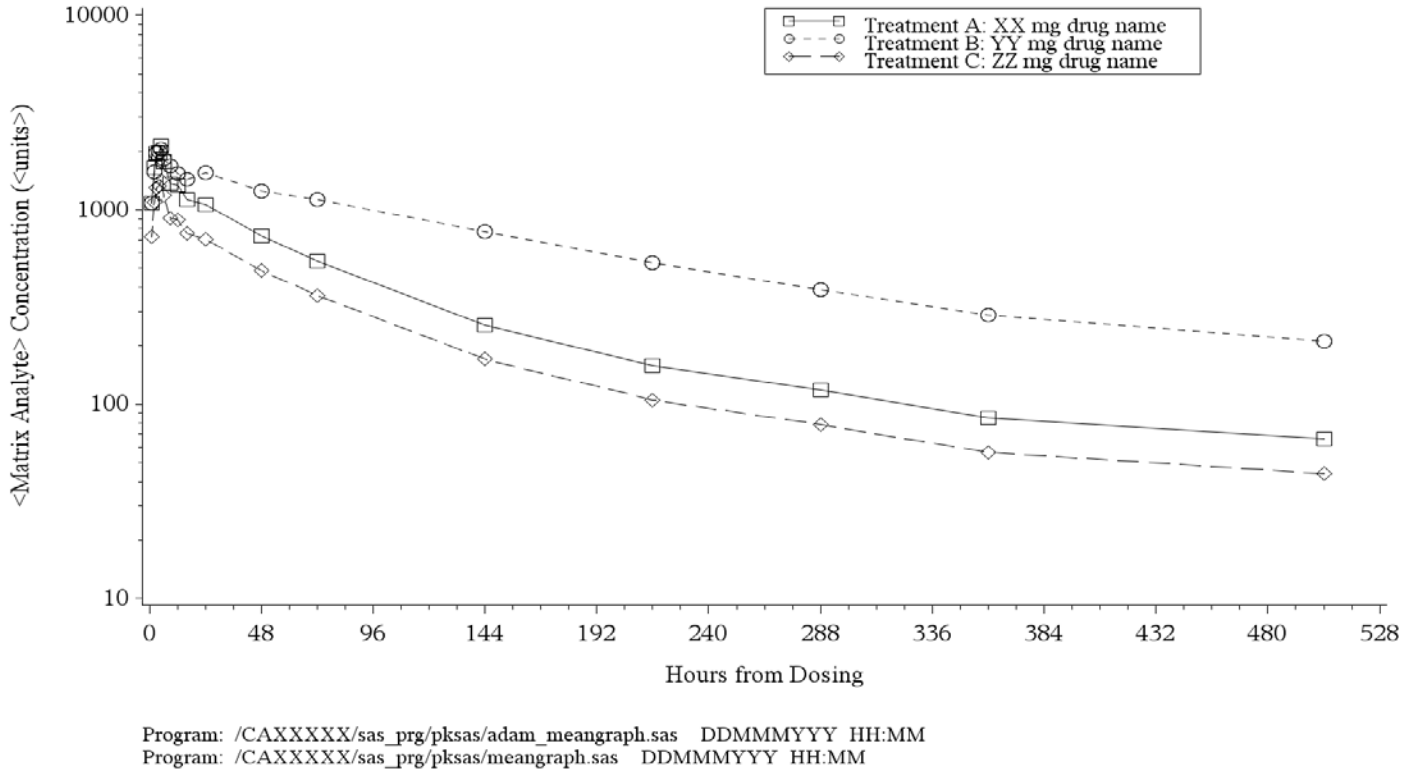


Programming note : the legend will present the 3 products ‘Product X: Product Description’

The x-axis title will be: ‘Time From Start of Product Use (min)’.

Figure PFPConc3 will be in the following RFT format :

Figure Mean Plasma Nicotine Concentrations Versus Time (Semi-Log Scale) (PK Population)

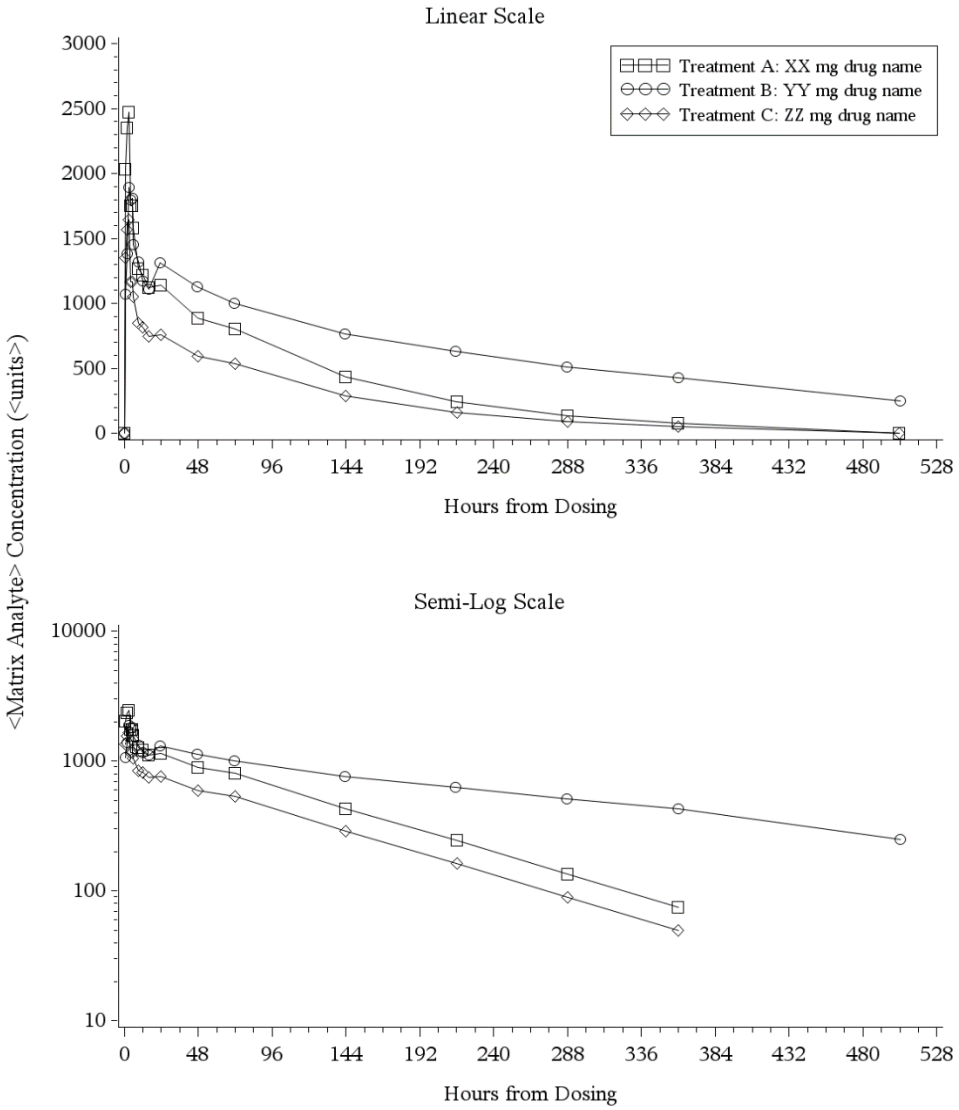


Programming note : the legend will present the 3 products 'Time From Start of Product Use (min)'
The x-axis title will be: 'Time From Start of Product Use (min)'

Linear and Semi-log Figures in Appendix 16.2.6.1 will have the following format:

Appendix 16.2.6.1

Individual Plasma Nicotine Concentrations Versus Time (Linear and Semi-Log Scales)



Program: /CAXXXXX/sas_prg/pksas/adam_indgraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/indgraph-all.sas DDMMMYYY HH:MM

Programming note : the legend will present the 3 products.
The x-axis title will be: 'Time From Start of Product Use (min)'
The y-axis title will be: 'Plasma Nicotine Concentration (ng/mL)'

12.3 Section 14 Summary Tables Shells

Table CDS Disposition Summary (Safety Population)

Category	Overall
Screened	XXX
Enrolled	XX
Enrolled and Exposure to P1 Product	XX
Randomized	XX (100%)
Completed Study	XX (XX%)
Discontinued From Study	X (XX%)
<Reason>	X (XX%)

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1programname2022Q1.sas DDMMMYYYY HH:MM

Table SDS Subject Product Use Status and Study Disposition (Safety Population) (Safety Population)

Subject Number	Randomized Product Sequence	Product Administrated			Study Completion	
		P1R	P1M	CIG	Status	Date
X	XXXXXXXXXX	Yes	No	Yes	Discontinued From Study: <Reason>	DDMONYYYY
X	XXXXXXXXXX	Yes	Yes	Yes	Completed Study	DDMONYYYY
X	XXXXXXXXXX	Yes	Yes	Yes	Completed Study	DDMONYYYY
X	XXXXXXXXXX	Yes	Yes	Yes	Completed Study	DDMONYYYY
		XX	XX	XX		

Programmer Note: Please refer to Section 5 for the product description.

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CDEM Demographic Summary (Safety Population)

Sex	Trait	Category/Statistic	Overall
All	Sex	Male	X (XX%)
		Female	X (XX%)
	Race	Asian	X (XX%)
		Black or African American	X (XX%)
		White	X (XX%)
	Ethnicity	Hispanic or Latino	X (XX%)
		Not Hispanic or Latino	X (XX%)
	Age (yr)	n	X
		Mean	X.X
		SD	X.XX
		Minimum	XX
		Median	X.X
		Maximum	XX
	Body Mass Index (kg/m^2)	n	X
		Mean	X.X
		SD	X.XX
		Minimum	XX
		Median	X.X
		Maximum	XX

Descriptive statistics for body mass index, height, and weight are calculated using screening measurements.

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer note: If there is at least a difference of 1 subject between the safety, Randomized, and PK, and populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis. The summarization for each sex will also be presented.

Table CUB Tobacco/Nicotine-Containing Product Use History Summary (Safety and PK Population)

Sex	Question	Product	Answer	Overall
All	Have you smoked continuously for the past 3 years?	Manufactured or roll-your-own cigarettes	Yes	X(XX.X%)
			No	X(XX.X%)
		Cigars/cigarillos	Yes	X(XX.X%)
			No	X(XX.X%)
		XXXXXXX		
	In the last 4 weeks, on average how many of these products did you smoke/use per day?	Manufactured or roll-your-own cigarettes	1 cigarette or less	X(XX.X%)
			2 to 5 cigarettes	X(XX.X%)
			6 to 9 cigarettes	X(XX.X%)
			10 to 19 cigarettes	X(XX.X%)
			1 to 2 packs	X(XX.X%)
			More than 2 packs	X(XX.X%)
	Do you plan to quit smoking cigarettes within the next 3 months?		Yes	X(XX.X%)
			No	X(XX.X%)
	Do you plan to stop using tobacco and/or nicotine containing products within the next 3 months?		Yes	X(XX.X%)
			No	X(XX.X)

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

Programmer Note: All products (Manufactured or roll-your-own cigarettes, Cigars/cigarillos, Tobacco Pipe, Smokeless tobacco products, E-vapour products), and Nicotine replacement therapy (NRT) products in the tobacco/nicotine use history will be included in the descriptive statistics table. Number of years smoked will be presented using descriptive statistics. If there is at least a difference of 1 subject between the safety, Randomized, and PK, and populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis. The summarization for each sex will also be presented.

Table CSU Usual Brand Cigarettes Summary (Safety and PK Population)

Sex	Trait	Category/Statistic	Overall
All	Substance	XXXXX	X (XX%)
		XXXXXXXXXXX	X (XX%)
	Amount	n	X
		Mean	X.X
		SD	X.XX
		Minimum	XX
		Median	X.X
		Maximum	XX
	Brand	XXXXXXXXXX	X (XX%)
		XXXXXXXXXXXXXXXXXXXXXXXXX	X (XX%)
		XXXXX	X (XX%)
	Brand Style	XXXXXXXX	X (XX%)
		XXXXXXXXXXXXXXXXXXX	X (XX%)
	Flavour	XXXXXXXXXX	X (XX%)
		XXXXXXXXXXXXXXXXXXXXXXXXX	X (XX%)
	Cigarette Length	XXXXXXXX	X (XX%)
		XXXXXXXXXXXXXXXXXXX	X (XX%)

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer note: If there is at least a difference of 1 subject between the safety, Randomized, and PK, and populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis. The summarization for each sex will also be presented.

Table CFT Fagerström Test for Nicotine Dependence Summary (Safety and PK Population)

Sex	Trait	Category/Statistic	Overall
All	Fagerstrom Score	n	X
		Mean	X.X
		SD	X.XX
		Minimum	XX
		Median	X.X
		Maximum	XX
	Nicotine Dependence Level	Mild (0-3)	X (XX%)
		Moderate (4-6)	X (XX%)
		Severe (7-10)	X (XX%)

Program: /CAXXXXX/ sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Programmer note: If there is at least a difference of 1 subject between the safety, Randomized, and PK, and populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis. The summarization for each sex will also be presented.

Note: Plasma Nicotine Concentration Tables (CPCONC1) will have the following format:

Page 1 of X

Table Plasma Nicotine Concentrations (ng/mL) Following THS Regular stick (P1R) (PK Population)

Subject Number	Product Sequence	Sex	Pre-use	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
n			X	X	X	X	X	X	X	X	X	X	X
n missing			X	X	X	X	X	X	X	X	X	X	X
% n missing			X	X	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	X.X	X.X
SD			X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
95% CI			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-X,X	X.X-X,X	X.X-X,X	X.X-X,X
Minimum			XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
1st quartile			X.X	X.X	X.X	X.X	X.X	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	X.X	X.X	X.X	X.X	X.X
3rd quartile			X.X	X.X	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	XX	XX

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

Programming Notes: For the 95% CI (of Mean), the lower and upper limits may be presented on different rows if the space limit requires it.
If there is at least a difference of 1 subject between the Randomized and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.
The number and percent of values below LLOQ or above ULOQ are to be presented in each summary table. If 50% or more data are below LLOQ or above ULOQ, only the number and percent of values below LLOQ or above ULOQ is to be reported in the summaries, together with minimum (= LLOQ/2) and maximum (= ULOQ) of the observed values.

Footnotes to include under the table, as appropriate:
<. = Concentration value missing or not reportable.>
<Concentration values that were below the limit of quantitation (BLQ) of 0.200 ng/mL were set to one-half of the limit of quantitation for the calculation of summary statistics.>

Sample Times are listed in Section 6.1. Descriptive statistics precision is specified in Section 6.4.

Note: Plasma Nicotine Pharmacokinetic Parameter Tables (CPPAR1) will have the following format:

Table Plasma Nicotine Pharmacokinetic Parameters Following THS Regular stick (P1R) (PK Population)

Subject Number	Product Sequence	Sex	Parameters: Parm 1 <unit>	Parm 2 <unit>	Parm 3 <unit>	Parm 4 <unit>	Parm X <unit>
XX	XXXXXX	X	X.XX	X.XX	X.XX	X.XX	X.XX
XX	XXXXXX	X	X.XX	X.XX	X.XX	X.XX	X.XX
XX	XXXXXX	X	X.XX	X.XX	X.XX	X.XX	X.XX
n			X	X	X	X	X
n missing			X	X	X	X	X
% n missing			X	X	X	X	X
Mean			X.X	X.X	X.X	X.X	X.X
SD			X.XX	X.XX	X.XX	X.XX	X.XX
95% CI of Mean			X.XX-XX.XX	(repeat format for other parameters)			
Minimum			XX	XX	XX	XX	XX
1st quartile			X.X	X.X	X.X	X.X	X.X
Median			X.X	X.X	X.X	X.X	X.X
3rd quartile			X.X	X.X	X.X	X.X	X.X
Maximum			XX	XX	XX	XX	XX
Geom. Mean			X.X	X.X	X.X	X.X	X.X
Geom. CV%			XX.X	XX.X	XX.X	XX.X	XX.X
95% CI of Geom. Mean			X.XX-XX.XX	(repeat format for other parameters)			

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

Programming Notes: Footnote to include under the table, as appropriate: <. = Parameter value missing or not reportable.>
If there is at least a difference of 1 subject between the Randomized and PK populations, a column for population will be added as the first column and the summary statistics will be presented for each population with table title updated to reflect the populations used in the analysis.
The plasma nicotine PK parameters are Cmax (ng/mL), Tmax (min), AUC0-24 (ng*min/mL), AUC0-Tmax (ng*min/mL).
Geometric mean, geometric CV% and 95% CI of Geom. Mean will be calculated only for Cmax, AUC0-24, and AUC0-Tmax.
For Tmax, only median, Q1, Q3, minimum and maximum will be presented.
Descriptive statistics precision is specified in Section 6.3.

Note: Statistical comparison of PK parameters (CPStat1) will have the following format:

Table Statistical Comparison of Plasma Nicotine Pharmacokinetic Parameters Cmax, AUC0-24, and AUC0-Tmax (PK Population)

Comparison	Parameter	Geometric LS Means: Test (n)	Geometric LS Means: Comparator (n)	% Geometric LS Mean Ratio (Test/Comparator)	90% Confidence Interval	p-value
P1R vs CIG	Cmax	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	AUC0-24	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	AUC0-Tmax	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
P1M vs CIG	Cmax	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	AUC0-24	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	AUC0-Tmax	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

P1R = < >
P1M = < >
CIG = < >
The mixed model includes sequence, period, product as fixed effects and subject as a categorical random effect modeling the within subject correlations.
Parameters are ln-transformed prior to analysis
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means from the ANOVA.
% Geometric LS Mean Ratio = 100*(Test/Comparator)
Test = The first product in the comparison
Comparator = The second product in the comparison
n = Number of observation used in the analysis

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

Programming note: Geometric LS Means to be presented to same precision as Mean in the PK parameter table. Geometric Mean Ratio and 90% confidence intervals will be presented to 2 decimal places; p-value will be presented to 4 decimals.

Note: Statistical comparison of PK parameter Tmax (CPStat2) will have the following format:

Table Statistical Comparison of Plasma Nicotine Pharmacokinetic Parameter Tmax (PK Population)

		Difference <X> - <Y>	
Parameter	Median	90% Confidence Interval	p-value
Tmax	X.XX	-X.XXXX - X.XXXX	X.XXXX

Product: <Label for First Product >
Product: <Label for Second Product>

Notes for Generating the Actual Table:

Presentation of Data:

- Median difference will be presented to 2 decimals or 3 significant figures
- 90% CI will be presented to 4 decimals
- p-value will be presented to 4 decimals

Programmers Note:

The comparisons will be: P1R vs CIG and P1M vs CIG, where P1R = THS regular stick; P1M = THS menthol stick; and CIG = Combustible cigarette. Add column identifying the comparisons.

The difference between products (product effect) and the 95% confidence interval for the difference was calculated using Hodges-Lehmann estimator.

Program: DM_PX:[HLXXXXX.PKSAS]XXXX.SAS DDMMMYYYY HH:MM

Note: Summary table (CPD1) will have the following format:

Table CPD1 Summary of VAS Craving Assessment by Study Product and Time Point (PK Population)

			Product		
Time Point	Sex	Statistic	P1R	P1M	CIG
XXXXXXXXXXXXXXX	Female	n	X	X	X
		Mean	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX
		CV(%)	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX
		1st quartile	X.X	X.X	X.X
		Median	X.X	X.X	X.X
		3rd quartile	X.X	X.X	X.X
		Maximum	XX	XX	XX
		95% CI	X.X-X.X	X.X-X.X	X.X-X.X
	Male	n	X	X	X
		Mean	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX
		CV(%)	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX
		1st quartile	X.X	X.X	X.X
		Median	X.X	X.X	X.X
		3rd quartile	X.X	X.X	X.X
		Maximum	XX	XX	XX
		95% CI	X.X-X.X	X.X-X.X	X.X-X.X

P1R: < >
P1M: < >
CIG: < >

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

Programmer Note: All collection time points and overall (sex combined) for each timepoint will also be presented in the table.

Table CAEO Overall Product Use Emergent Adverse Event Frequency by Study Product – Number of Subjects Reporting the Event
(% of Subjects Used Study Product) (Safety Population)

		Product Administration				
Adverse Event	Admission (N = X)	P1R (N = X)	P1M (N = X)	CIG (N = X)	Overall (N = X)	SFU (N = X)
Number of Subjects With PUEAEs	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)
Number of Subjects With SAEs	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)
Number of Subjects With IP Events	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)
Number of Subjects With AEs Leading to Discontinuation	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)
Number of Subjects With AEs Leading to Death	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)
Number of Subjects With AEs Related to IP	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)

P1R: < >
P1M: < >
CIG: < >
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.
PUEAEs = Product use-emergent adverse events; SAEs = Serious adverse events; IP = Investigational product
Admission = after ICF and prior to the product test on Day 1
SFU = after discharge from CRU to safety follow-up visit

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CAES Product Use Emergent Adverse Event Frequency by Study Product – Number of Subjects Reporting the Event
(% of Subjects Used Study Product) (Safety Population)

		Product Administration				
Adverse Event	Admission (N = X)	P1R (N = X)	P1M (N = X)	CIG (N = X)	Overall (N = X)	SFU (N = X)
Number of Subjects With PUEAEs	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)
Number of Subjects Without PUEAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Eye disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vision blurred	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal and connective tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Back pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Muscle cramps	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nervous system disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Headache	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Reproductive system and breast disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vaginal discharge	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Epistaxis	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

P1R: < >
P1M: < >
CIG: < >
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.
Adverse events are classified according to MedDRA Version 25.1.
PUEAEs = Product use-emergent adverse events
Admission = after ICF and prior to the product test on Day 1
SFU = after discharge from CRU to safety follow-up visit

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

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

		Product Administration				
Adverse Event	Admission (N = X)	P1R (N = X)	P1M (N = X)	CIG (N = X)	Overall (N = X)	SFU (N = X)
Number of PUEAEs	X (X%)	X (XX%)	X (XX%)	X (X%)	X (XX%)	X (XX%)
Eye disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vision blurred	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal and connective tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Back pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Muscle cramps	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nervous system disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Headache	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Reproductive system and breast disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vaginal discharge	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Epistaxis	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

P1R: < >
P1M: < >
CIG: < >
Adverse events are classified according to MedDRA Version 25.1.
PUEAEs = Product use-emergent adverse events
Admission = after ICF and prior to the product test on Day 1
SFU = after discharge from CRU to safety follow-up visit

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

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

Adverse Event	Product	Number of Subjects With PUEAEs	Number of PUEAEs	Severity			Relationship to Study Product		Relationship to Study Procedure	
				Mild	Moderate	Severe	Unrelated	Related	Unrelated	Related
Abdominal pain	XXX	X	X	X	X	X	X	X	X	X
Constipation	XXX	X	X	X	X	X	X	X	X	X
Dry throat	XXX	X	X	X	X	X	X	X	X	X
Dysmenorrhoea	XXX	X	X	X	X	X	X	X	X	X
Dyspepsia	XXX	X	X	X	X	X	X	X	X	X
Headache	XXX	X	X	X	X	X	X	X	X	X
	XXX	X	X	X	X	X	X	X	X	X
Myalgia	XXX	X	X	X	X	X	X	X	X	X
Nasal congestion	XXX	X	X	X	X	X	X	X	X	X
Skin laceration	XXX	X	X	X	X	X	X	X	X	X
	Admission	X	X	X	X	X	X	X	X	X
	P1R	X	X	X	X	X	X	X	X	X
	P1M	X	X	X	X	X	X	X	X	X
	CIG	X	X	X	X	X	X	X	X	X
	Overall	X	X	X	X	X	X	X	X	X
	FU	X	X	X	X	X	X	X	X	X

P1R: < >
P1M: < >
CIG: < >
Adverse events are classified according to MedDRA Version 25.1.
PUEAEs = Product use-emergent adverse events
Admission = after ICF and prior to the product test on Day 1
SFU = after discharge from CRU to safety follow-up visit
Overall = From the product use on Day 1 through the discharge from CRU.

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table 14.3.2.1 Serious Adverse Events (Safety Population)

Will match format of Appendix 16.2.7

Or contain statement as follows:

"There were no events that met this criteria."

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CLBO Out-of-Range Values and Recheck Results - <Clinical Laboratory Panel> (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)
X	XX/X	Screen			DDMMMYYYY	HH:MM:SS	XX HN		XX LN G1	XX HN
		1	-X	-X.XX	DDMMMYYYY	HH:MM:SS	XX LN	XX LY-		XX LN

Programmer Note: 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. Unscheduled and Early Termination records should only be included if they are out of range or recheck results.

F = Female; M = Male
H = Above reference range; L = Below reference range
CS Flag: N = Not clinically significant; Y = Clinically significant
PI interpretation: - = Not clinically significant
CTCAE grade (Version 5.0): G1 = Mild

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CLBS Clinically Significant Laboratory and Corresponding Results (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Department	Test	Result	Reference Range	Unit
X	XX/X	1	X	-X.X	DDMMMYYYY	HH:MM	Serum Chemistry	Cholesterol	XXX	X – X	mg/dL

Programmer Note: All time points for a subject/test with at least one value deemed as CS by the PI will be presented in this table.

H = Above reference range
Computer: Y = Clinically significant
PI Interpretation: R = Recheck requested, + = Clinically significant

If no event meet this criteria then include a statement as follows:

"There were no clinical laboratory results documented as clinically significant by the PI."

Table CLBD Clinical Laboratory Summary and Change From Baseline - <Clinical Laboratory Panel> (Safety Population)

					Randomized Product Sequence					
Laboratory Test (units)	Reference Range	Time Point		Statistic	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)
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
		Discharge	Absolute	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

Programmer Note: Means at specific time points will be flagged (with a *) if they are above or below the reference range. This only applies to the clinical laboratory results (i.e., not the change from baseline or any other endpoints). Time Point column will match those found in Section 8.9 of the SAP.

P1R: < >
P1M: < >
CIG: < >
Baseline is the last measurement collected prior to the first product administration.
= Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1 for the breakdown.
* = Above reference range; ^ = Below reference range
Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CLBS Clinical Laboratory Shift From Baseline - Serum Chemistry (Safety Population)

			Baseline L			Baseline N			Baseline H		
			Post Use			Post Use			Post Use		
Laboratory Test (units)	Randomized Product Sequence	Time Point	L	N	H	L	N	H	L	N	H
Testname (unit)	XXX	Discharge	X	XX	X	X	XX	X	X	XX	X
	XXX	Discharge	X	XX	X	X	XX	X	X	XX	X
	XXX	Discharge	X	XX	X	X	XX	X	X	XX	X
	XXX	Discharge	X	XX	X	X	XX	X	X	XX	X
	XXX	Discharge	X	XX	X	X	XX	X	X	XX	X
	XXX	Discharge	X	XX	X	X	XX	X	X	XX	X

Programmer Note: For urinalysis, the following footnote is used since the categories of N and O will be used instead of L, N, H:
N = Within reference range; O = Outside reference range

P1R: < >
P1M: < >
CIG: < >
Baseline is the last measurement collected prior to the first product administration.
N = Within reference range; L = Below reference range; H = Above reference range

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CVS Vital Sign Summary and Change From Baseline (Safety Population)

				Randomized Product Sequence					
Vital Sign (units)	Time Point		Statistic	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)
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 2	Absolute	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

P1R: < >
P1M: < >
CIG: < >
Baseline is the last measurement collected prior to the first product administration.

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CEG 12-Lead Electrocardiogram Summary and Change From Baseline (Safety Population)

				Randomized Product Sequence					
Measurement (units)	Time Point		Statistic	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)
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
	Discharge	Absolute	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

P1R: < >
P1M: < >
CIG: < >
Baseline is the last measurement collected prior to the first product administration.

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

Table CSP Spirometry Summary and Change From Baseline (Safety Population)

				Randomized Product Sequence					
Measurement (units)	Time Point		Statistic	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)	XXX (N = X)
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
	Discharge	Absolute	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

P1R: < >
P1M: < >
CIG: < >
Baseline is the last measurement collected prior to the first product administration .

Program: /CAXXXXX/sas_prg/stsas/tab/programname2022Q1.sas DDMMMYYYY HH:MM

13. 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 generated from data created in accordance with SDTM Model 1.4 with Implementation Guide 3.2 or CDASH data structure. Listings with derived data may be created from the ADaM data. All listings will be presented in Courier New size font 9. Time point information (period, day, hour) will match that found in the CRF.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Reference Range	Unit
Serum Chemistry	Testname1	MALE		XX - XXX	mEq/L
	Testname2	MALE	0-25	XX - XXX	U/L
			26-99	XX - XXX	U/L
<similar for all other tests, note that age will only be presented when different reference range exists>					
Hematology	<similar to serum chemistry>				
Urinalysis	Testname	MALE		NEGATIVE	
Urine Drug Screening	Amphetamines	MALE		NOT DETECTED	

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.1.1 Subject Disposition (Safety Population)

		Prematurely Discontinue From All Study Administration				End of Study			
Subject Number	Randomized/ Actual Product Sequence	Did Subject Prematurely Discontinue?	Administration Discontinuation Date	Primary Administration Discontinuation Reason	Specify	Did Subject Complete the Study?	Date/Time of Last Contact	Primary Study Discontinuation Reason	Specify
1	XXX/XXX	No				Yes	DDMMMYYYY HH:MM		
2	XXX/XXX	No				No	DDMMMYYYY HH:MM	Personal Reason	XXXXX
3	XXX/X	Yes	DDMMMYYYY	Adverse Event	XXXXXXXXXXX	No	DDMMMYYYY HH:MM	Other	XXXXX

P1R: THS regular stick
P1M: THS menthol stick
CIG: Combustible cigarette

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.1.2 Subject Disposition (Screen Failures)

	End of Study			
Subject Number	Did Subject Complete the Study?	Date of Completion or Discontinuation	Primary Study Discontinuation Reason	Specify
1	No	DDMMMYYYY	XXXXXXXXXXXXXXXX	
2	No	DDMMMYYYY	XXX XXXXX	
3	No	DDMMMYYYY	Other	XXXXX

P1R: THS regular stick
P1M: THS menthol stick
CIG: Combustible cigarette

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.4.2 will resemble the format of Appendix 16.2.4.1.

Appendix 16.2.4.1 Demographics (Safety Population)

Subject Number	Year Of Birth	Age (yr)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	Body Mass Index (kg/m²)
1	YYYY	47	Male	< >	Not Hispanic or Latino	XXX	XX.X	XX.XX
2	<similar to above.							

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.4.4 will resemble the format of Appendix 16.2.4.3.

Appendix 16.2.4.3 Informed Consent (Safety Population)

Subject	Informed Consent			Informed Re-consent		
Number	Date	Time	Protocol Version	Date	Time	Protocol Version
1	DDMMMYYYY	HH:MM	XXXXXXXXXXXXXX	DDMMMYYYY	HH:MM	XXXXXXXXXXXXXX
2	<similar to above.					

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.4.6 will resemble the format of Appendix 16.2.4.5.

Appendix 16.2.4.5 Physical Examination (I of II) (Safety Population)

Subject Number	Study Period	Date	Was Physical Exam Performed?	System1	System2	System3	System4	System5	System6
X	Screen	DDMMMYYYY	Yes	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL

* = See Appendix 16.2.4.7 Physical Examination Description
HEENT = Head, Eyes, Ears, Nose, Throat

Program: /CAXXXX/sas_prg/stsas/programname2022Q1.sas DDMMMYYYY HH:MM

Appendix 16.2.4.6 Physical Examination Descriptions (Safety Population)

Subject Number	Study Period	Date	System	Result	Description or Comment
X	Screen	DDMMMYYYY	Skin	ABNORMAL	RIGHT CHEST SCAR-NCS

HEENT = Head, eyes, ears, nose, throat

Program: /CAXXXX/sas_prg/stsas/programname2022Q1.sas DDMMMYYYY HH:MM

Appendix 16.2.4.8 Medical History (Safety Population)

Subject Number	Any History?	Condition or Event	System Organ Class	Preferred Term	Date		
					Start	End	Ongoing?
1	No						
2	Yes	< >	XXXXXXXXX	XXXXXXXXX	YYYY		YES

<note date can be YYYY, MONYYYY, or DDMONYYYY based on individual subject data>

Medical history are classified according to MedDRA Version 25.1.

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.4.9 Tobacco/Nicotine-Containing Product Use History (Safety Population)

Subject Number	Study Period	Was Assessment Completed?	Date	Time	Product	Have You Smoked/Used Continuously for at Least the Past 3 Years?	In the Last 4 Weeks, on Average How Many of These Products did You Smoke/Use per Day?
X	Screen	XXX	DDMMMYYYY	HH:MM	XXXXXXX	XXX	XXXXXXXXXXXXXXXXX

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.4.10 Usual Brand Cigarettes Documentation (Safety Population)

Subject Number	Study Period	Substance	Start Date	Stop Date	Amount	Brand	Brand Style	Flavour	Cigarette Length
X	Screen	XXX	DDMMMYYYY	DDMMMYYYY	XXX	XXXXXXXXX	XXXXXXX	XXXXXXX	XXXXXXXXXX

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.4.11 Fagerström Test for Nicotine Dependence (Safety Population)

Subject Number	Study Period	Was Assessment Completed?	Date	Time	Question* 1	2	3	4	5	6	Total Score	Classification of Nicotine Dependence#
X	XXXX	XXX	DDMMMYYYY	HH:MM	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	X	XXXXXXXXXX

* 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 prohibited?
  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 awakening than during the rest of the day?
  6 = Do you smoke even if you are so sick that you are in bed most of the day?
#Classification score range: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points)

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.5.1 Subject Enrollment (Safety Population) (Safety Population)

Subject Number	Study Period	Study Day	Was the Subject Enrolled?	Criterion Type (Inclusion, Exclusion, Other)	Criterion ID Not Met	If Other, Specify
1	1	-X	YES	XXXXX		

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.5.3 will resemble the format of Appendix 16.2.5.2.

Appendix 16.2.5.2 Subject Eligibility (Safety Population)

Subject Number	Study Period	Did subject meet all eligibility criteria?	Criterion Not Met	Specify
1	Screen	YES		
2	Screen	NO	Exclusion 5	<specify and criterion not met will only be presented if populated>

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.5.4 Randomization (Safety Population)

Subject Number	Study Period	Study Day	Randomization Date	Randomization Time	Was the Subject Randomized?	Randomization sequence
X	XXXX	XXX	DDMMMYYYY	HH:MM	XXXX	XXXXXXXXXX

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.5.5 Investigational Product Administration (Safety Population)

Subject Number	Study Period	Product	Day	Interval	Product Use Date	Product Use Start Time	Product Use Stop Time	Planned Product and Unit	Comments
1	1	XXX	1	XX-XX	DDMMMYYYY	HH:MM:SS	HH:MM:SS	XXXXXXXX	XXXXXXXX

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.5.6 Prior and Concomitant Medications (Safety Population)

Subject Number	Product	Prior?	Medication (WHO DD)	Dosage	Route	Start Date	Start Time	End Date	End Time	Frequency	Indication	Ongoing?
1			None									
2			None									
3		Yes	CETIRIZINE (CETIRIZINE)	X MG	BY MOUTH	DDMONYYYY		DDMONYYYY	HH:MM	XXXXXXX	XXXXXXX	NO
	XXX	No	PARACETAMOL (PARACETAMOL)	X MG	XXXXXXXXX	DDMONYYYY	HH:MM	XXXXXXXXX	HH:MM	XXXXXXXX	XXXXXXXX	XX

P1R: < >
P1M: < >
CIG: < >
Concomitant medications are coded with WHO Drug Dictionary Version 01SEP2022 b3.
WHO DD = World Health Organization Drug Dictionary
Prior is defined as a medication administered prior to the first study product administration.

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.5.7 Plasma Nicotine Pharmacokinetic Blood Draw Times and Concentration Data (Safety Population)

Subject Number	Period	Study Product	CRF Day	CRF Timepoint	Blood Draw Date	Blood Draw Time	Elapsed Time From Last Product Use (minutes)	Measured Concentration (ng/mL)	Comment
1	1	P1R	1	XXXXX	DDMONYYYY	HH:MM:SS	0.00	X.XX	
				XXXXX	DDMONYYYY	HH:MM:SS	X.XX	X.XX	
				XXXXX	DDMONYYYY	HH:MM:SS	X.XX	X.XX	
			< >						

<similar for all other time points and subjects>

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/pksas/standardlis/pk_bld.sas DDMMMYYYY HH:MM
Programmer Notes:

- Population: Safety population will be used in this listing.

Appendix 16.2.6.2 VAS Craving Assessment (Safety Population)

Subject Number	Study Period	Study Product	Study Day	Study Hour	Date	Was Event Performed?	VAS Score	Comment
X	X	XXX	XXXX	X.XX	DMMMYYYY	XXX	XXX	

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.6.3 VAS Liking Assessment (Safety Population)

Subject Number	Study Period	Study Product	Study Day	Study Hour	Date	Was Event Performed?	VAS Score	Comment
X	X	XXX	XXXX	X.XX	DMMMYYYY	XXX	XXX	

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.6.4 Intention to Use Again (Safety Population)

Subject Number	Study Period	Study Product	Study Day	Study Hour	Date	Was Event Performed?	VAS Score	Comment
X	X	XXX	XXXX	X.XX	DMMMYYYY	XXX	XXX	

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.7.1 Adverse Events (Safety Population)

Subject Number	Age/ Sex	Product	PUE?	System Organ Class/ Preferred Term (Verbatim)	Time From Last Use (DD:HH:MM)	Date:Time Start/ End Duration (DD:HH:MM)	Serious/ Outcome	Severity/ Frequency	Study Product Relationship/ Action/ Other Action	Study Procedure Relationship/ Expectedness
1	30/F			None						
2	24/M			None						
3	52/M	XXX	Yes	XXXXXXXXXXXX/ XXXXXXXXXXXXXXXX (XXXXXXXXXXX)	XX:XX:XX	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15	No/ Recovered/ Resolved	Moderate/ Intermittent	Related/ XXXXXXX/ XXXXXXXXXX	Unrelated/ Expected
		XXX	Yes	<similar to above>						
4	XX/M	SFU	Yes	XXXXXXXXXXXX/ XXXXXXXXXXXXXXXX (XXXXXXXXXXX)	XX:XX:XX	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15	No/ Recovered/ Resolved	Moderate/ Intermittent	Related/ XXXXXXX/ XXXXXXXXXX	Unrelated/ Expected

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

P1R: < >
P1M: < >
CIG: < >
Adverse events are classified according to MedDRA Version 25.1
PUE = Abbreviation for product use-emergent
F = Female; M = Male
SFU = after discharge from CRU to safety follow-up visit

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.7.2 Details for Serious Adverse Events (Safety Population)

Subject Number	Age/ Sex	Product	PUE?	System Organ Class/ Preferred Term (Verbatim)	Date:Time Start/ End Duration (DD:HH:MM)	Serious Event?	Congenital Anomaly/ Birth Defect?	Persistent or Significant Disability or Incapacity?	Hospital-ization?	Life-Threat?	Important Medical Event?	Death?
3	52/M	P1R	Yes	XXXXXXXXXXX/ XXXXXXXXXXXXXXXXX (XXXXXXXXXXX)	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15	Yes	No	No	Yes	No	Yes: < >	No

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

P1R: < >
P1M: < >
CIG: < >
Adverse events are classified according to MedDRA Version 25.1.
PUE = Abbreviation for product use-emergent
F = Female; M = Male
SFU = after discharge from CRU to safety follow-up visit

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.7.3 Product Events (Safety Population) (Safety Population)

Subject Number	Age/ Sex	Product	Any Events?	Date	Time	Device Number	Affected Part	Severity	Event Category	Description of Product Event/ Complaint	Was Pharmacy Informed?	Was a New Device Dispensed?	New Device Serial Number
3	52/M	P1R	Yes	DDMMMYYYY	HH:MM:SS	XXXX	XXXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXXX

P1R: < >
P1M: < >
CIG: < >

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendices 16.2.8.2 – 16.2.8.5 will resemble 16.2.8.1.

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

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Chloride M: 97-105 (mEq/L)	Potassium M: 3.7-5.2 (mEq/L)	Phosphorus M: 2.4-4.4 (mg/dL)	Sodium M: 135-143 (mEq/L)
1	XX/M	Screen			DDMONYYYY	HH:MM:SS	XXX	X.X	X.X	XXX HY- G1
		1	1	-17.00	DDMONYYYY	HH:MM:SS	XXX HN	X.X	X.X	XXX HN
		Recheck			DDMONYYYY	HH:MM:SS	XXX	X.X	X.X	XXX
	<similar to above for all subjects/time points>									

F = Female; M = Male
H = Above reference range
CS flag: N = Not clinically significant; Y = Clinically significant
PI interpretation: - = Not clinically significant
CTCAE grade (Version 5.0): G1 = Mild

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.8.6 Alcohol Breath Test (Safety Population)

Subject Number	Age/ Sex	Study Period	Date	Time	Result & Unit	Comment
1	XX/M	Screen	DDMONYYYY	HH:MM:SS	XXX XXX	
<similar to above for all subjects/time points>						

F = Female; M = Male

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.8.7 Vital Signs (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Blood Pressure (mmHg) Position	Blood Pressure (mmHg) Sys/Dia	Pulse (bpm)	Respiration (brpm)	Temperature (°C)	Weight (kg)
1	30/F	Screen			DDMONYYYY	HH:MM:SS						XX.X
							SUP5	XXX/ XX	XX	XX	XX.X	
					R	HH:MM:SS	SUP5	XXX/ XX				
					R	HH:MM:SS	SUP5	XXX/ XX				
		1	-1	-17.0	DDMONYYYY	HH:MM:SS	SUP5	XXX/ XX				

F = Female; M = Male
SUP5 = 5-minute supine; R = Recheck value; brpm = breaths/min

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.8.8 12-Lead Electrocardiogram (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Result	Heart Rate (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTcF (msec)	Specify/Comments
1	30/F	Screen			DDMONYYYY	X:XX:XX	WNL	XX	XX	XX	XXX	XXX	EARLY REPOLARIZATION; LEFT AXIS DEVIATION
		1	-1	X.XX	DDMONYYYY	XX:XX:XX	ANCS	XX	XX	XX	XXX	410	LEFT AXIS DEVIATION
		3	X	X.XX	DDMONYYYY	XX:XX:XX	< >	XX	XX	XX	XXX	451	SINUS BRADYCARDIA

F = Female; M = Male
R = Recheck value; WNL = Within normal limits; ANCS = Abnormal, not clinically significant
QTcF = QT corrected for heart rate using Fridericia's correction

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM

Appendix 16.2.8.9 Spirometry (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	15?/ 1h?	FVC (L)	FVC Predicted (%)	FEV1 (L)	FEV1 Predicted (%)	FEV1/FVC Ratio	Abnormal?	If Abnormal, Indicate if CS/NCS	Comment
1	30/F	Screen			DDMONYYYY	HH:MM	Y/Y	XX	XX	XX	XXX	XXX	X		
		1	X	X.X	DDMONYYYY	HH:MM	Y/Y	XX	XX	XX	XXX	XXX	X		

F = Female; M = Male
NCS = Not clinically significant; CS = Clinically significant
15? = Did subject rest for at least 15 minutes in sitting position?
1h? = Did subject not use cigarettes for at least 1 hour?

Program: /CAXXXXX/sas_prg/stsas/lis/programname2022Q1.sas DDMONYYYY HH:MM