A Randomised, Cross-Over, Nicotine Pharmacokinetic and Pharmacodynamic Study of Heated Tobacco Products Compared to Combustible Cigarettes

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Statistical analysis plan - FINAL version 1.0 13/Jan/2022

STATISTICAL ANALYSIS PLAN

A Randomised, Cross-Over, Nicotine Pharmacokinetic and Pharmacodynamic Study of Heated Tobacco Products Compared to Combustible Cigarettes

Imperial Brands PLC Project No. NER01/0004
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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Protocol: NER01/0004

Study Title: A Randomised, Cross-Over, Nicotine Pharmacokinetic and Pharmacodynamic Study of Heated Tobacco Products Compared to Combustible Cigarettes

Issue Date: 13 January 2022

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1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from this study. Any changes made from the planned analysis within protocol, after locking of the database will be documented in the clinical study report (CSR). The section referred to as Table and Figure Shells within this SAP describes the traceability of the tables, figures, and listings (TFLs) back to the data.

Any additional exploratory analyses not addressed within this SAP and/or driven by the data, or requested by Imperial Brands PLC, will be considered out of scope and must be approved by Imperial Brands PLC and described in the CSR.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary

1. To evaluate and compare the C_{max} and AUC_t of nicotine after the use of each Heated Tobacco (HT) product or combustible cigarettes (CCs) comparator.

Secondary

1. To evaluate other pharmacokinetic (PK) parameters of nicotine after the use of each HT product or CCs comparator.

2. To evaluate the reduction in smoking urges observed after the use of each HT product or CCs comparator.

3. To evaluate product perception and preference by use of subjective assessments.

4. To evaluate the tolerability and safety of each of the products used.

5. To investigate usage behaviour for each product using measurements of topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter puff interval) for each product.

2.2 Study Endpoints, Key Assessments, and Summarization

Pharmacokinetics:

For each morning product use session on Days 1 through 4, plasma nicotine PK parameters (AUC_{inf}, AUC_{0-90}, AUC_{0-240}, AUC_t, C_{max}, C_{last}, T_{max}, $T_{1/2}$) will be computed from the individual plasma concentrations for each study product. Baseline adjustments will be performed.

Nicotine concentrations and PK parameters will be listed by subject and summarised using descriptive statistics.

Subjective Effects:

Intent to Use (ITU)

Descriptive statistics of the visual analog scale (VAS) will be provided by study product and product use session. Individual responses will be listed by subject.

Urge to Smoke

Responses and derived parameters (E_{max}, TE_{max}, $AUEC_{0-240}$) will be listed by subject and summarised using descriptive statistics.

Product Evaluation Scale

Responses will be considered as a 7-point scale, and will be presented as factors outlined in Section 9.2.

Descriptive statistics of the factors will be provided by study product and product use session. Individual responses will be listed.

Puff Topography:

Puff topography will be assessed using a SPA-M topography device. The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time. Topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average flow rate, inter-puff interval) will be listed by subject and summarised using descriptive statistics.

Product Use Behaviour:

All product use data, including the number HT sticks used and the number of CCs smoked (Days -1 through Day 4), will be summarised using descriptive statistics.

Incidence of device malfunction(s) will also be tabulated.

Safety:

Safety will be monitored in-study through physical examination (symptom-driven), vital signs measurements, ECGs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

Adverse Events (AEs) spontaneously reported by the subjects or observed by the Investigator or other study personnel will be monitored from Screening until the follow-up.

AEs will be tabulated and summary statistics for vital signs and clinical laboratory tests will be computed and provided, as deemed clinically appropriate.

3. STUDY DESIGN

This will be a randomised, cross-over, open-label, confinement study conducted in 24 adult male or female smokers of CCs. The study will investigate combustible and HT products in a cross-over design, incorporating PK evaluation, subjective questionnaire assessments, usage behaviour, puff topography, as well as safety evaluation.

Subjects will perform a screening visit and 1 study visit, including a 5-day confinement period and finally a follow-up telephone call approximately 7 days after the final product use.

Visit 1 (Screening)

Screening procedures will be performed within 27 days prior to study procedures on Day -1 and will include an eligibility check, review of health status and assessment of nicotine consumption habits. Medical and tobacco-use histories and demographic data will be collected. Other screening procedures include a physical examination (including oral cavity and oropharynx), vital signs, electrocardiogram (ECG), body mass index (BMI), clinical laboratory tests (hematology, serum chemistry, urinalysis), serology, urine/saliva drug, urine/breath alcohol, cotinine screen, exhaled carbon monoxide (CO), and pregnancy and follicle-stimulating hormone (FSH) tests (for females as appropriate). If required, subjects will be offered smoking cessation advice and contact information for a smoking cessation support service.

Visit 2 (In-clinic period, Day -1 to Day 4)

At Visit 2, subjects who successfully complete the screening procedures and meet all the inclusion criteria and none of the exclusion criteria will be eligible to check in to the clinical research unit (CRU) on Day -1 and will remain at the clinic until Day 4 for daily study product use, PK sampling, subjective questionnaire assessments, puff topography (as applicable), and safety assessments.

On Day -1, following eligibility confirmation, subjects will undertake a familiarisation session of the study products and questionnaires. The clinical team will explain how the HT products will be used. Subjects will have the opportunity to see the products/devices and packaging and will participate in a Product Trial where they will consume one HT stick (flavour chosen by subject). All products/devices used in the trial session will not be used in the clinical study but will be retained as demonstration samples for accountability purposes. An explanation of how the questionnaires will be administered to the subjects will be given. After the familiarisation session and completion of check-in procedures, subjects will be

allowed to smoke their own cigarettes *ad libitum* but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of the morning controlled product use session on Day 1.

In the morning of Day 1, after pre-use assessments and confirmation of eligibility, the subjects will be randomised to 1 of 4 product sequences and then provided a single product of the study product in the sequence to which they have been randomised. On Days 1 through 4, subjects will use the assigned study product (i.e., completely use a single unit of the assigned study product, with puffs taken at 30-second intervals and puffs 3 seconds in duration). PK samples will be collected within 5 minutes pre-study product use and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 120, and 240 minutes following the start of study product use. Questionnaires will be administered to the subject at defined intervals throughout the day. Safety will be monitored throughout the day.

On Days 1 through 4, following the 4-hour PK blood collection, subjects will start a 4-hour *ad libitum* product use session (no limits on cigarette or HT consumption) with the same study product used during the morning controlled use session.

On Days 3 and 4, puff topography will be performed during the last 2 hours of the 4-hour *ad libitum* product use session. The Sodim Smoking Puff Analyzer Mobile (SPA-M) topography device will collect data (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter-puff interval) for 2 hours. The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time.

The *ad libitum* product use session on Days 1 through 4 will start at approximately the same time each day, with lunch served at the start of the *ad libitum* product use session, at approximately the same time each day. After completion of the *ad libitum* use session, subjects will be allowed to smoke their own cigarettes (*ad libitum*) but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of the morning controlled product use scheduled on the following day.

A new/unused device will be provided to the subjects on each day of HT product use (i.e., the same device will be used for the morning controlled product use and *ad libitum* product use sessions on the same day).

On Day 4, following completion of study assessments, subjects will be allowed to use their own cigarettes and will leave the CRU after completing all final check out requirements.

Visit 3 (Follow-up phone call)

A follow-up telephone call (Visit 3) will be made by the CRU in an attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 7 days after the final product use to determine if any AE has occurred since the last study visit

4. SAMPLE SIZE ESTIMATION

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives.

5. SUBJECT RANDOMISATION

Subjects who complete the study screening assessments and meet all the eligibility criteria and are randomised will be assigned a unique randomisation identification number on Day 1 and will receive study products according to the randomisation scheme.

Subjects will be randomized into 1 of 4 sequences (ABCD, BDAC, CADB, and DCBA).

6. ANALYSIS POPULATIONS

Safety Population will include all subjects who have successfully completed eligibility requirements after checking in to the CRU and used at least one study product including subject's OBCC.

Outcomes Population will include a subset of the safety population and will consist of subjects who used a study product and have evaluable PK, subjective effects, or topography data. This population will be used in the summary and analysis of PK, subjective effects, topography, and product use, and all available data will be included in the summary tables to the extent possible.

7. STUDY PRODUCT DESCRIPTIONS

All subjects will use Products A through D

The following products will be tested in this study:

Study Product	Short Description	Long Description
A	[redacted]	[redacted]HT device with[redacted] American Blend stick
B		[redacted]HT device with [redacted]
C		[redacted]HT device with [redacted] stick
D	Subjects OBCC	Subject's own brand combustible cigarette (OBCC)

8. PHARMACOKINETIC ANALYSIS

8.1 Measurements and Collection Schedule

On each of Days 1, 2, 3 and 4, venous blood samples (~4 mL per sample) for PK analysis of plasma nicotine concentrations will be collected at time 0 (approximately 5 minutes prior to the start of product use) and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 120 and 240 minutes, relative to the start of product use.

8.2 Bioanalytical Method

Plasma nicotine will be analyzed by LC-MS/MS at Celerion Bioanalytical Services Lincoln, Nebraska, using validated analytical methods with appropriate quality controls according to the Food and Drug Administration (FDA) Guidance for Industry (Title 21 CFR Part 58). Additionally, processing of samples will completed by a non-tobacco user.

8.3 Pharmacokinetic Concentrations

For the concentration tables, unadjusted plasma nicotine concentrations that are BLQ will be set to one-half of the lower limit of quantitation for the calculation of descriptive statistics.

Individual nicotine concentrations will be adjusted for baseline nicotine ("baseline-adjusted") and all PK parameters will be calculated based on the adjusted concentrations. Baseline adjustment will be performed by subtraction of the pre-existing nicotine concentration from each nicotine concentration obtained after test product administration in that period/day for each subject using the following equation:

$$C_t = C_{t\ unadjusted} - [C_0 \cdot e^{-Kel \cdot t1}]$$

where C_t is the adjusted concentration at time t, $C_{t\ unadjusted}$ is the observed concentration at time t, C_0 is the pre-product use concentration (-5 minutes), $Kel = \frac{\ln(2)}{t½}$, t½ is 2 hours (average nicotine half-life), t is the actual sampling time since product administration, and t1 is the actual sampling time since the time of the pre-product use sample.

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

Baseline-adjusted plasma nicotine concentrations will be used for the calculation of the plasma nicotine PK parameters.

All concentration data will be included in the calculation of the individual PK parameters, the individual concentration-time plots (based on actual sample times), and in the mean concentration-time plots (based on nominal sample times). However, if there are any significant deviations from nominal sample times, some concentration data may be excluded from the descriptive statistics and the mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be listed and discussed in the CSR.

8.4 Noncompartmental Pharmacokinetic Analysis and Parameter Calculation

The appropriate noncompartmental PK parameters will be calculated from the baseline-adjusted plasma nicotine concentration-time data using Phoenix® WinNonlin® Version 8.1 or higher. Actual sample times will be used in the calculations of the PK parameters. The calculation of the actual time for plasma nicotine will be in respect to the start of product use. All PK parameters included in the protocol are listed in Table 8.1 below, and are defined as appropriate for study design.

Table 8.1. Noncompartmental Pharmacokinetic Parameters to be Calculated

Parameter	Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
AUC_{0-90}	AUC0-90	Area under the baseline-adjusted nicotine concentration-time curve from time zero (defined as the start of the product use session) to the 90-minutes time point. If the 90-minutes plasma concentration is missing, BLQ, or not reportable, then interpolation and/or extrapolation will be conducted, as appropriate. If interpolation and/or extrapolation cannot be reliably performed, then this parameter cannot be calculated.	Calculated using the Linear Trapezoidal with Linear Interpolation Method

Parameter	Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
AUC_{0-240}	AUC0-240	Area under the baseline-adjusted nicotine concentration-time curve from time zero (defined as the start of the product use session) to the to the 240-minutes time point. If the 240-minutes plasma concentration is missing, BLQ, or not reportable, then interpolation and/or extrapolation will be conducted, as appropriate. If interpolation and/or extrapolation cannot be reliably performed, then this parameter cannot be calculated.	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC_t	AUCt	Area under the baseline-adjusted nicotine concentration-time curve from time zero (defined as the start of the product use session) to the time of the last measurable non-zero concentration.	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC_{inf}	AUCinf	Area under the baseline-adjusted concentration-time curve from time 0 extrapolated to infinity	Calculated as: $AUC_t + (C_{last}/ K_{el})$ where C_{last} is the last observed/measured concentration
$AUC_{\%extrap}$	AUC%extrap	Percent of AUC_{inf} extrapolated to infinity	Calculated as: $(1 – AUC_t/AUC_{inf}) \times 100$
C_{max}	Cmax	Maximum baseline-adjusted plasma concentration over the duration of the measurement interval.	Taken directly from bioanalytical data
Clast	Clast	Plasma baseline-adjusted nicotine concentration at last time point measured.	Taken directly from bioanalytical data
T_{max}	T_{max}	Time to reach the maximum baseline-adjusted plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the C_{max}

Parameter	Label to be Used in the Text, Tables and Figures	Definition	Method of Determination
$T_{½}$	T½	Apparent first-order terminal elimination half-life.	Calculated as ln2/K_{el}
K_{el}	Kel	Apparent first-order terminal elimination rate constant	Calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear period (e.g., three or more non-zero plasma concentrations).

Pharmacokinetic parameters will not be calculated for subjects with less than 3 consecutive post-product administration time points with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only and excluded from the summary statistics, statistical analysis, and mean profiles.

The K_{el} will be determined using linear regressions composed of least 3 data points. The K_{el} will not be calculated if 1) the terminal elimination phase is not apparent, 2) if C_{max} is one of the 3 last data points, or 3) if the R^2 value is less than 0.75. In cases where the K_{el} interval is not calculated, the values of T½ will not be reported.

8.5 Data Summarization and Presentation

SAS® software (Version 9.4) will be used for all data presentation and summarization including statistical analyses, summary tables, graphs, and data listings. Descriptive statistics will be generated for plasma concentrations and PK parameters.

The plasma nicotine concentrations will be listed for all subjects and presented with the same level of precision as received from the bioanalytical laboratory. Plasma nicotine concentrations will be summarised by study product for all subjects in the outcomes population, by sex and overall using descriptive statistics. Summary statistics, including sample size (n), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal time point for both baseline-adjusted and unadjusted concentrations. Excluded subjects or timepoints will be included in the concentration tables, but will be excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as “BLQ” in the concentration tables and footnoted accordingly.

Mean and individual concentration-time profiles will be presented on linear and semi-log scales. Linear mean plots will be presented with and without SD.

Plasma nicotine PK parameters will be listed and summarised by product (overall and by sex) for all subjects in the Outcomes Population. Pharmacokinetic parameters will be reported to 3 significant figures for individual parameters, with the exception of T_{max}, which will be presented with 2 decimal places. Summary statistics will be reported, including n, mean, SD, CV%, SEM, minimum, median, and maximum by study product (overall and by sex). In addition, geometric mean (geom mean) and geometric CV% (geom CV%) will be provided for the C_{max} and AUC parameters by study product (overall and by sex).

Excluded subjects or timepoints will be listed in the PK parameter tables, but will be excluded from the summary statistics and noted as such in the tables.

The level of precision for each concentration and PK parameter statistic will be presented as follows: minimum/maximum in same precision as in the bioanalytical data (concentrations) or as mentioned above for the PK parameters, mean/median/geom mean in one more level of precision than minimum/maximum, SD/SEM in one more level of precision than mean/median, n will be presented as an integer, CV% and geom CV% will be presented to the nearest tenth.

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

8.6 Statistical Analysis of PK Parameters

A linear mixed model for analysis of variance (ANOVA) will be performed on the natural log-transformed PK parameters C_{max} and AUCt following the morning product use session on each of Days 1, 2, 3, and 4. The model will include sequence, product, and study period as fixed effects and subject-nested-within-sequence as a random effect. Sequence will be tested using subject-nested-within-sequence as the error term for infomraitonal purposes. Geometric least-squares means (LSM) and 95% confidence intervals (CIs) will be provided for the PK parameters of C_{max} and AUCt by product. Geometric LSM ratio, 95% CIs of geometric LSM ratio, and p-values will be provided for the product comparisons in C_{max} and AUCt. The comparisons of interest will include each of the products compared to each other.

The above statistical analyses will be performed using the following SAS® code:

```
Proc mixed data=< >;
class subject sequence period product;
model  log(parameter) = sequence period product / ddfm=KR;
random  subject (sequence);
lsmeans product/diff cl alpha=0.05;
estimate “Product A versus Product D” Product 1 0 0 -1/cl alpha=0.05;
estimate “Product B versus Product D” Product 0 1 0 -1/cl alpha=0.05;
```

```
estimate “Product C versus Product D” Product 0 0 1 -1/cl alpha=0.05;
estimate “Product A versus Product B” Product 1 -1 0 0/cl alpha=0.05;
estimate “Product A versus Product C” Product 1 0 -1 0/cl alpha=0.05;
estimate “Product B versus Product C” Product 0 1 -1 0/cl alpha=0.05;
run;
```

Note: Protocol defined the study as Days 1-4 and the CRF had periods 1-4 (each have one day), respectively. Period will be used in the database and therefore in the statistical analysis.

Non-parametric analysis (Wilcoxon Signed Rank test) will be performed for the comparisons of T_{max} between each of the study products. Median difference and 95% CI of the difference will be presented for each comparison. The CI is constructed using Walsh Averages and the appropriate quantile of the Wilcoxon Signed Rank Test Statistic.

9. SUBJECTIVE MEASURES ANALYSIS

Subjective Effects Questionnaires

The Intent to Use (VAS), Urge to Smoke (VAS), and Product Evaluation Scale (7-point scale) questionnaires will be completed using a computerised tablet device. All relevant software specific to the electronic questionnaires will be provided by IVRCC ePro.

Subjects will be familiarised with the questionnaires on Day -1. An explanation of how the questionnaires will be administered to the subjects will be given. Responses will not be recorded.

All questionnaires will be completed at the time points delineated below. When scheduled at the same time as a PK blood draw, the Urge to Smoke questionnaire will be completed approximately 30 seconds prior to the scheduled blood draw (except for the one scheduled at Time 0, which will be performed approximately 10 minutes prior to the start of the product use session), and all other questionnaires will be completed within approximately 2 minutes after the last scheduled blood draw.

9.1 Urge to Smoke (UTS)

Urge to Smoke questionnaire will be completed at Time 0 (pre-product use) and at 4, 8, 15, 45, 60, 120, and 240 minutes relative to the start of product use on Days 1, 2, 3, and 4.

The following parameters will be calculated for the urge to smoke assessments:

Emax	The maximum change from baseline VAS score (VASpre-use - VASpost-use)

TEmax	Time of the Emax. If the maximum value occurs at more than one time point, TEmax will be defined as the first time point with this value.
$AUEC_{0-240}$	The area under the change from baseline VAS score versus time curve from time 0 to 240 minutes.

Baseline is the pre-product-use for each product use. Responses, change from baseline, and derived parameters will be listed by subject and summarised by product, by sex and overall using descriptive statistics, including n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% CI.

An appropriate statistical method, similar to the PK analysis detailed above, will be used to compare Urge to Smoke parameters (no data transformation). LSM and 95% CIs will be provided for the E_{max} and $AUEC_{0-240}$ by product. LSM difference, 95% CIs of LSM difference, and p-values will be provided for the product comparisons in E_{max} and $AUEC_{0-240}$. The comparisons of interest will include each of the products compared to each other.

9.2 Product Evaluation Scale (PES)

Intent to Use questionnaire will be completed at 240 minutes following the start of study product use on each of Days 1, 2, 3, and 4.

Product Evaluation will be considered as a 7-point scale. Responses will be presented as the following factor scores:

a) Satisfaction: average of the response scores from questions 1, 2, 3, and 12;

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

c) Aversion: average of the response scores from questions 9, 10, 16, and 18;

d) Relief: average of items 11, 13, 14, 15, and reversed for item 20 (i.e., not at all = 7, extremely = 1);

e) Items 17, 19, 21 will be summarised as individual item scores.

Descriptive statistics of the factor scores will be provided by product, by sex and overall. Individual responses will be listed by subject.

9.3 Intent to Use (ITU)

Intent to Use questionnaire will be completed at 240 minutes following the start of study product use on each of Days 1, 2, 3, and 4.

Ratings of the subjects' If available, how likely are you to buy your assigned study product in the future?' recorded on a 100 mm VAS scale ranging from "Not at all" (0) to "Extremely" (100) will be reported.

In addition, responses to ITU questionnaire will also be treated as a bipolar variable. The bipolar score will be calculated by subtracting 50 from the original VAS score, then categorizing into three categories: -50 to < 0, 0, and > 0 to 50.

Descriptive statistics of the VAS raw score and bipolar score will be provided by product. Individual responses will be listed by subject. Frequency count table will be presented for the categories of the bipolar scores.

10. PUFF TOPOGRAPHY

On Days 3 and 4 only, puff topography measurements will be performed for 2 hours during the last 2 hours of the 4-hour *ad libitum* product use session. The topography session will span a 2-hour period and the SPA-M topography device will be stopped and restarted with each new stick or cigarette during that time.

The topography parameters listed in Table 10.1 and Table 10.2 will be assessed:

Table 10.1 Human Puffing Topography Parameters Per-Puff

Description	Variable	Unit
Puff number	Ni	
Puff duration	Di	s
Puff volume	Vi	mL
Peak puff flow rate	Qci	mL/s
Average puff flow rate	Qmi	mL/s
Inter-puff interval	Ii	s

Table 10.2 Human Puffing Topography Parameters Per-Product Use Experience

Description	Variable	Formula	Unit
Total number of puffs	NPC	ΣN_i	
Total puff volume	TVOL	ΣV_i	mL
Average puff volume	$AvgV_i$	ΣV_i / NPC, i=1 ... NPC	mL
Average puff duration	$AvgD_i$	ΣD_i / NPC, i=1 ... NPC	s
Total puff duration	TD_i	ΣD_i	s
Average flow rate	$AvgQm_i$	ΣQm_i / NPC, i=1 … NPC	mL/s
Average peak flow rate	$AvgQc_i$	ΣQc_i / NPC, i=1 … NPC	mL/s
Total inter puff interval	TI_i	ΣI_i	s
Average inter puff interval	$AvgI_i$	ΣQc_i / NPC, i=1 … NPC	s

Topography parameters will be listed by subject and summarised by product, sex, and overall using descriptive statistics, including n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% CI.

An appropriate statistical method, similar to the PK analysis detailed above, will be used to compare per product topography parameters (no data transformation). LSM and 95% CIs will be provided for the topography parameters by product. LSM difference, 95% CIs of LSM difference, and p values will be provided for the product comparisons in topography parameters. The comparisons of interest will include each of the products compared to each other.

11. PRODUCT USE BEHAVIOUR

On Days 1, 2, 3, and 4, subjects will use the product assigned according to the randomisation scheme under controlled conditions followed by a 4-hour *ad libitum* product use session with the same study product. Each subject will be provided with a new/unused Pulze HT device for each day of HT product use. The time each product is dispensed will be documented; products that stop functioning will be replaced and the failure documented.

The number of cigarettes smoked, as appropriate, will be documented from Check-in until beginning of smoking abstinence (Day -1, until at least 12 hours prior to the start of morning controlled product use on Day 1; Days 1 through 3, 8 hours post morning controlled use session IP start until at least 12 hours prior to the start of morning

controlled product use scheduled on the following day). The number of cigarettes smoked and the number of HT sticks used will be documented during each 4-hour ad libitum product use session (Days 1 through 4).

The number of inhalations and reasons for missed puffs will be documented, as applicable.

The number of HT sticks used (*ad libitum* product use session), the number of CCs smoked (Days -1 through 4), and the number of puffs (morning controlled product use session) will be listed by subject and summarised by product, sex, and overall using descriptive statistics, including n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% CI.

12. SAFETY

All case report form (CRF) data will be listed by subject and chronologically by assessment time points. This will include rechecks, unscheduled assessments, and early termination.

Applicable continuous variables will be summarised 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 summarised based on reduced denominators.

12.1 Subject Discontinuation

The number of subjects enrolled, number who completed the study, and number who did not complete the study (overall and reasons for early withdrawal) will be tabulated by randomised sequence and overall. The number of subjects who received each study product and who did not receive study product at each study day will be tabulated. Subjects only enrolled in the product trial and dropped prior to randomisation will be summarised separately.

12.2 Demographics

Descriptive statistics will be reported for continuous variables (age, weight, height, and BMI) and frequency counts will be tabulated for categorical demographics variables (sex, ethnicity, and race). Summarization will be done by randomised sequence and overall. Subjects only enrolled in the product trial and dropped prior to randomisation will be summarised separately. Screen failure subjects will be listed.

Age will be derived by subtracting the year of birth from the year of informed consent. If year of informed consent – year of birth is less than the protocol minimum age then the age derivation will be year of informed consent – year of birth +1.

12.3 Smoking History and Usual Brand Attributes

Smoking history and usual brand attributes will be summarised with descriptive statistics for continuous variables. Frequency counts will be presented for categorical variables. The continuous variables will include number of cigarettes smoked per day, number of years of cigarettes smoked, and the categorical variables will include usual cigarette brand, brand style, and flavour. Subjects only enrolled in the product trial and dropped prior to randomisation will be summarised separately.

12.4 Adverse Events

AE will be coded (to the preferred term) with Medical Dictionary for Regulatory Activities (MedDRA®) Version 24.1.

A study product use-emergent adverse event (PUEAE) is defined as an AE that is starting or worsening at the time of or after study product administration. Each PUEAE will be attributed to a product based on the onset date and time of the AE. AEs occurring prior to the first product use episode on Day 1 but after the product trial has started on Day -1 will be attributed to the product trial.

All events captured in the database will be listed in by-subject data listings. However, only PUEAEs will be summarised.

Frequencies of subjects with PUEAEs, regardless of relationship to study product will be summarised by study product and sorted by system organ class and preferred term. The number of PUEAEs will be tabulated in a similar manner. Tables which summarize the number of PUEAEs and number of subjects with PUEAEs by severity and relationship to study product will also be included.

Subjects only enrolled in the product trial and dropped prior to randomisation will be summarised separately.

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

12.5 Clinical Laboratory Tests (Serum Chemistry, Hematology, Urinalysis)

Clinical laboratory evaluations will be performed at Screening, Day -1, and at End-of-Study (EOS) or upon early termination.

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

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by assessment time point except for screening. Change from baseline will be summarised in a similar manner. Baseline is defined as the result closest and prior to the first product use on Day 1 which may include unscheduled or recheck results. This will typically be the result collected 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.

For each laboratory test, a shift table will be developed to compare the frequency of the results at baseline (above normal, normal, or below normal) with the respective post product use results. For urinalysis tests, the categories are normal and outside normal

12.6 Vital Signs

Vital signs (blood pressure, heart rate, respiration rate, and body temperature) will be measured for safety purposes at Screening, Check-in (Day -1), prior to the product use on Days 1-4, and at EOS or upon early termination.

Descriptive statistics will be reported for vital sign measurements (blood pressure, heart rate, respiration rate, and body temperature) by time point except for screening. Change from baseline will be summarised in a similar manner. Baseline is defined as the result closest and prior to the first product use on Day 1 which may include unscheduled or recheck results. This will typically be the result collected prior to study product use 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.

12.7 Electrocardiogram

Electrocardiogram will be performed at Screening, Day -1, and at EOS or upon early termination.

Descriptive statistics will be presented for each ECG parameter by assessment time point except for screening. Change from baseline will be summarised in a similar manner. Baseline is defined as the result closest and prior to the first product use on Day 1 which may include unscheduled or recheck results. This will typically be the result collected 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.

ECG data will be listed by subject and assessment timepoint. QTcF values that are > 450 msec and increase from baseline > 30 msec will be flagged in the data listing.

12.8 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary Version 01SEP2021 b3 and listed.

12.9 Oral and Physical Examination

Oral and physical examinations will be performed at Screening. Symptom-driven physical examinations may be performed at other times, at the Investigator or designee's discretion. Physical examinations will be listed by subject. Abnormal findings will be discussed in the CSR.

12.10 Exhaled CO

Exhaled CO will be performed at Screening and Day -1.

Exhaled CO data will be listed by subject and assessment timepoint.

12.11 Device Malfunction

Incidence of device malfunction(s) will be listed by subject and tabulated by product.

13. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

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

- Per protocol, the summarization of puff topography parameters will be based on by study product, study day, overall and by sex, usual brand cigarette flavour (non-menthol or menthol), age, number of years smoking, CPD, and time point. Some of the variables are not applicable for summarization of topography parameters. The topography parameters will be summarised by study product, sex, and overall.

14. SUMMARY TABLES AND FIGURES

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

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 Section 14 Tables and Figures

14.1 Demographic Data Summary Tables

Table 14.1.1	Summary of Disposition (Safety Population)
Table 14.1.2	Disposition of Subjects (Safety Population)
Table 14.1.3	Demographic Summary (Safety Population)
Table 14.1.4	Smoking History and Usual Brand Attributes Summary (Safety Population)

14.2 PK, Subjective Measures, and Product Use Behaviour Summary Tables and Figures

14.2.1 Pharmacokinetic Tables – Plasma Nicotine

Table 14.2.1.1	Unadjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Intense American Blend Stick (Outcomes Population)
Table 14.2.1.2	Unadjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Regular American Blend Stick (Outcomes Population)
Table 14.2.1.3	Unadjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Regular Menthol Stick (Outcomes Population)
Table 14.2.1.4	Unadjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Subjects OBCC (Outcomes Population)
Table 14.2.1.5	Baseline-Adjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Intense American Blend Stick (Outcomes Population)
Table 14.2.1.6	Baseline-Adjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Regular American Blend Stick (Outcomes Population)
Table 14.2.1.7	Baseline-Adjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Regular Menthol Stick (Outcomes Population)

Table 14.2.1.8	Baseline-Adjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use of Subjects OBCC (Outcomes Population)
Table 14.2.1.9	Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters) Following Controlled Product Use of Intense American Blend Stick (Outcomes Population)
Table 14.2.1.10	Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters Following Controlled Product Use of Regular American Blend Stick (Outcomes Population)
Table 14.2.1.11	Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters Following Controlled Product Use of Regular Menthol Stick (Outcomes Population)
Table 14.2.1.12	Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters Following Controlled Product Use of Subjects OBCC (Outcomes Population)
Table 14.2.1.13	Intervals (Minutes) Used for the Determination of Baseline-Adjusted Plasma Nicotine Kel Values (Outcomes Population)
Table 14.2.1.14	Statistical Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters Cmax and AUCt Following Controlled Product Use (Outcomes Population)
Table 14.2.1.15	Statistical Comparison of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters Cmax and AUCt Following Controlled Product Use (Outcomes Population)

14.2.2 Pharmacokinetic Figures – Plasma Nicotine

Figure 14.2.2.1	Mean (SD) Unadjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Linear Scale) (Outcomes Population)
Figure 14.2.2.2	Mean Unadjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Linear Scale) (Outcomes Population)

Figure 14.2.2.3	Mean Unadjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Semi-Log Scale) (Outcomes Population)
Figure 14.2.2.4	Mean (SD) Baseline-Adjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Linear Scale) (Outcomes Population)
Figure 14.2.2.5	Mean Baseline-Adjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Linear Scale) (Outcomes Population)
Figure 14.2.2.6	Mean Baseline-Adjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Semi-Log Scale) (Outcomes Population)

14.2.3 Subjective Measures Tables

Urge to Smoke Tables

Table 14.2.3.1.1	Summary of Urge to Smoke VAS Scores During and After the Controlled Product Use by Product (Outcomes Population)
Table 14.2.3.1.2	Summary of Urge to Smoke VAS Scores Difference from Pre-use During and After the Controlled Product Use by Product (Outcomes Population)
Table 14.2.3.1.3	Summary of Urge to Smoke VAS Parameter During and After the Controlled Product Use by Product (Outcomes Population)
Table 14.2.3.1.4	Statistical Summary of Urge to Smoke Parameters Emax and AUEC0-240 Following Controlled Product Use (Outcomes Population)
Table 14.2.3.1.5	Statistical Comparison of Urge to Smoke Parameters Emax and AUEC0-240 Following Controlled Product Use (Outcomes Population)

PES Subscales Tables

Table 14.2.3.2	Summary of PES Factor Scores by Study Product for Controlled Product Use (Outcomes Population)

Future Intent to Use VAS Score Tables

Table 14.2.3.3.1	Frequency of Responses to Future Intent to Use in Each Category by Product for Controlled Product Use (Outcomes Population)
Table 14.2.3.3.2	Summary of Future Intent to Use (VAS Score) in Each Category by Product for Controlled Product Use (Outcomes Population)
Table 14.2.3.3.3	Summary of Future Intent to Use (VAS Raw Scores) by Product for Controlled Product Use (Outcomes Population)

14.2.4 Puff Topography Tables

Table 14.2.4.1	Summary of Per-Product Puff Topography Parameters by Product and Overall (Outcomes Population)
Table 14.2.4.2	Statistical Summary of Per-Product Puff Topography Parameters Following Ad Libitum Product Use (Outcomes Population)
Table 14.2.4.2	Statistical Comparison of Per-Product Puff Topography Parameters Following Ad Libitum Product Use (Outcomes Population)

14.2.5 Product Use Behaviour Tables

Table 14.2.5.1	Summary of Total Number of HT Sticks Used During the Ad Libitum Product Use by Product (Safety Population)

Table 14.2.5.2	Summary of Total Number of CC Smoked on Days -1 through 4 During the Ad Libitum Product Use (Safety Population)
Table 14.2.5.3	Summary of Total Number of Puffs During the Controlled Product Use by Product (Safety Population)

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Table 14.3.1.1	Adverse Event Frequency by Product – Number of Subjects Reporting the Event (% of Subject Who Received Study Product) (Safety Population)
Table 14.3.1.2	Adverse Event Frequency by Product – Number of Adverse Events (% of Total Adverse Events) (Safety Population)
Table 14.3.1.3	Adverse Event Frequency by Product, Severity, and Relationship to Study Product – Number of Subjects Reporting the Event (Safety Population)
Table 14.3.1.4	Adverse Event Frequency by Product, Severity, and Relationship to Study Product – Number of Adverse Events (Safety Population)

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1	Serious Adverse Events (Safety Population) (if no serious adverse event occurred, a statement ‘There were no serious adverse event recorded during the study.’)

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

Table 14.3.4.1	Out-of-Range Values and Recheck Results – Serum Chemistry (Safety Population)
Table 14.3.4.2	Out-of-Range Values and Recheck Results – Hematology/Coagulation (Safety Population)
Table 14.3.4.3	Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)

14.3.5 Display of Clinical Laboratory and Vital Signs

Table 14.3.5.1	Clinical Laboratory and Change From Baseline Summary – Serum Chemistry (Safety Population)
Table 14.3.5.2	Clinical Laboratory Shift From Baseline – Serum Chemistry (Safety Population)
Table 14.3.5.3	Clinical Laboratory and Change From Baseline Summary – Hematology (Safety Population)
Table 14.3.5.4	Clinical Laboratory Shift From Baseline – Hematology (Safety Population)
Table 14.3.5.5	Clinical Laboratory and Change From Baseline Summary – Urinalysis (Safety Population)
Table 14.3.5.6	Clinical Laboratory Shift From Baseline – Urinalysis (Safety Population)
Table 14.3.5.7	Vital Sign and Change From Baseline Summary (Safety Population)
Table 14.3.5.8	Electrocardiogram and Change From Baseline Summary (Safety Population)
Table 14.3.5.9	Incedence of Device Malfunction by Product (Safety Population)

14.2 Section 16 Data Listings

Note: Hepatitis and HIV results that are provided by the clinical laboratory will not be presented in subject data listings and will not be included in any database transfer.

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

Appendix 16.1.9	Statistical Methods
Appendix 16.1.10.1	Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Appendix 16.2.1	Subject Disposition (Safety Population)

16.2.2 Protocol Deviations

Appendix 16.2.2	Protocol Deviations

16.2.3 Subjects Excluded from Pharmacokinetic, Subjective Effects, Product Use Behaviour, and Pharmacodynamic Analysis

Appendix 16.2.3	Subjects Excluded from Pharmacokinetic, Subjective Effects, Product Use Behaviour, and Pharmacodynamic Analysis

Note: Appendices 16.2.2 and 16.2.3 are generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Appendix 16.2.4.1	Demographics (Safety Population)
Appendix 16.2.4.2	Oral/Physical Examination (I of II) (Safety Population)
Appendix 16.2.4.3	Oral/Physical Examination (II of II) (Safety Population)
Appendix 16.2.4.4	Medical History (Safety Population)
Appendix 16.2.4.5	Smoking History and Usual Brand Attributes (Safety Population)

16.2.5 Compliance and/or Product Use Data

Appendix 16.2.5.1	Subject Eligibility (Safety Population)
Appendix 16.2.5.2	Product Trial (Safety Population)
Appendix 16.2.5.3	Product Descriptions
Appendix 16.2.5.4	Product Use (Safety Population)
Appendix 16.2.5.5	Ad Lib Smoking (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, Subjective Measures Response, Product Use Behaviour, and Heart Rate Data

Appendix 16.2.6.1	Individual Unadjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Linear and Semi-Log Scales) (Outcomes Population)
Appendix 16.2.6.2	Individual Baseline-Adjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Linear and Semi-Log Scales) (Outcomes Population)
Appendix 16.2.6.3	Urge to Smoke (Safety Population)
Appendix 16.2.6.4	Urge to Smoke Parameters (Safety Population)
Appendix 16.2.6.5	Product Evaluation Scale Collection (Safety Population)
Appendix 16.2.6.5	Product Evaluation Scale Item Score (Safety Population)
Appendix 16.2.6.7	Product Evaluation Scale Factor Score (Safety Population)
Appendix 16.2.6.8	Intent to Use (Safety Population)
Appendix 16.2.6.9	Puff Topography Parameters – Per-Puff (Safety Population)
Appendix 16.2.6.10	Puff Topography Parameters – Per-Product (Safety Population)
Appendix 16.2.6.11	Product Use Behaviour (Safety Population)

16.2.7 Adverse Events Listings

Appendix 16.2.7.1	Adverse Events (Safety Population)
Appendix 16.2.7.2	Details for Serious Adverse Events (Safety Population)
Appendix 16.2.7.3	Device Malfunction (Safety Population)

16.2.8 Listings of Individual Laboratory Measurements and Other Safety Observations

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 Screen (Safety Population)
Appendix 16.2.8.5	Carbon Monoxide Breath Test (Safety Population)
Appendix 16.2.8.6	Vital Signs (Safety Population)
Appendix 16.2.8.7	12-Lead Electrocardiogram (Safety Population)

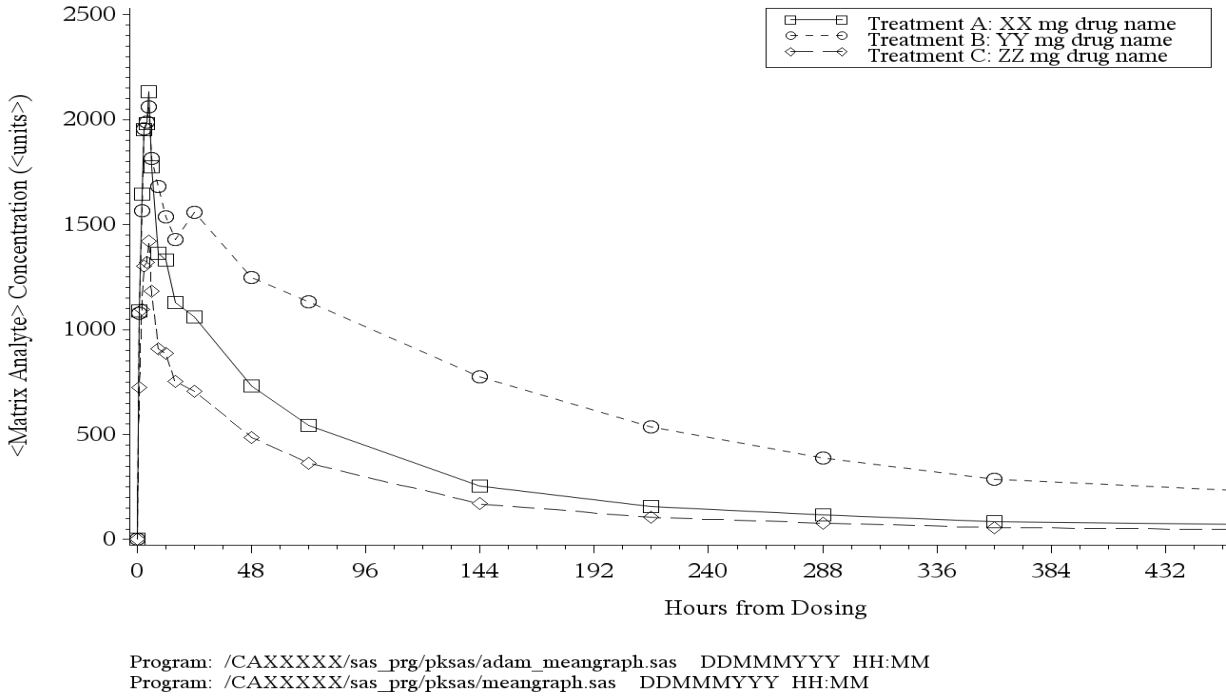
15. TABLE AND FIGURE SHELLS

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 all post-text tables will be presented in Courier New font size 9. These tables will be generated off of the Celerion ADaM data structure. ADaM datasets are created in accordance with CDISC guidance (ADaM Model 2.1 and ADaM implementation guide 1.1).

15.1 Figure Shells

Figure 14.2.2.2 and 14.2.2.5 will have the following format:
Internal template: Figure PFPConc2

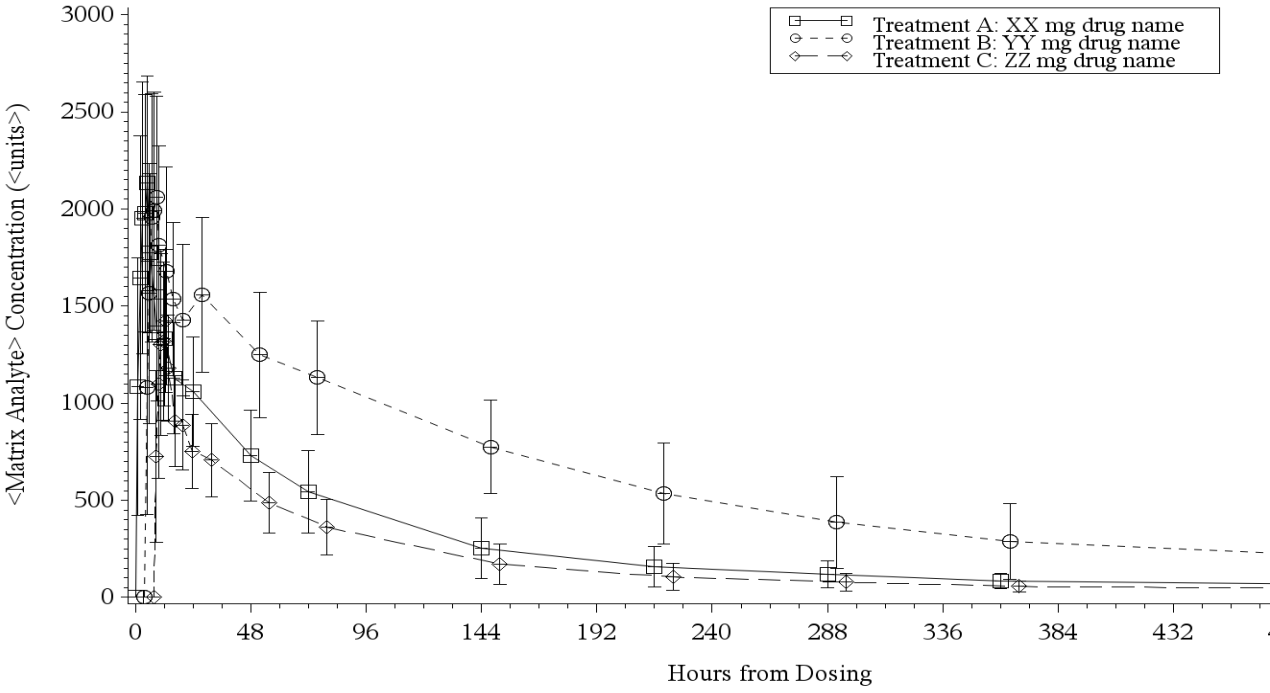
Figure 14.2.2.2 Mean Unadjusted Plasma Nicotine Concentrations Versus Time Following Contr
(Linear Scale) (Outcomes Population)



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

Figure 14.2.2.1 and 14.2.2.4 will have the following format:
Internal template: Figure PFPConc1

Figure 14.2.2.1 Mean (SD) Unadjusted Plasma Nicotine Concentrations Versus Time Following Contr
(Linear Scale) (Outcomes Population)

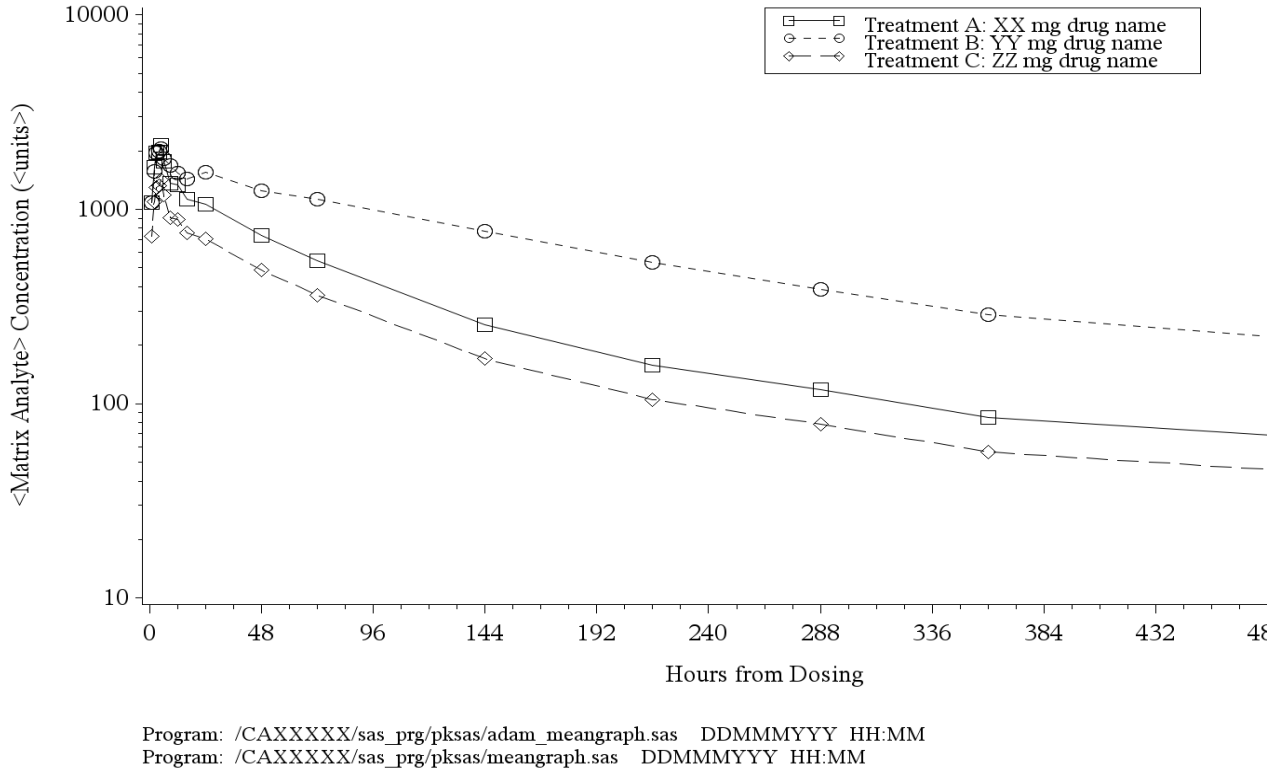


Treatments B and C are shifted to the right for ease of reading
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYY HH:MM

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

Figure 14.2.2.3 and 14.2.2.6 will have the following format:
Internal template: Figure PFPConc3

Figure 14.2.2.3 Mean Unadjusted Plasma Nicotine Concentrations Versus Time Following Controlled (Semi-Log Scale) (Outcomes Population)

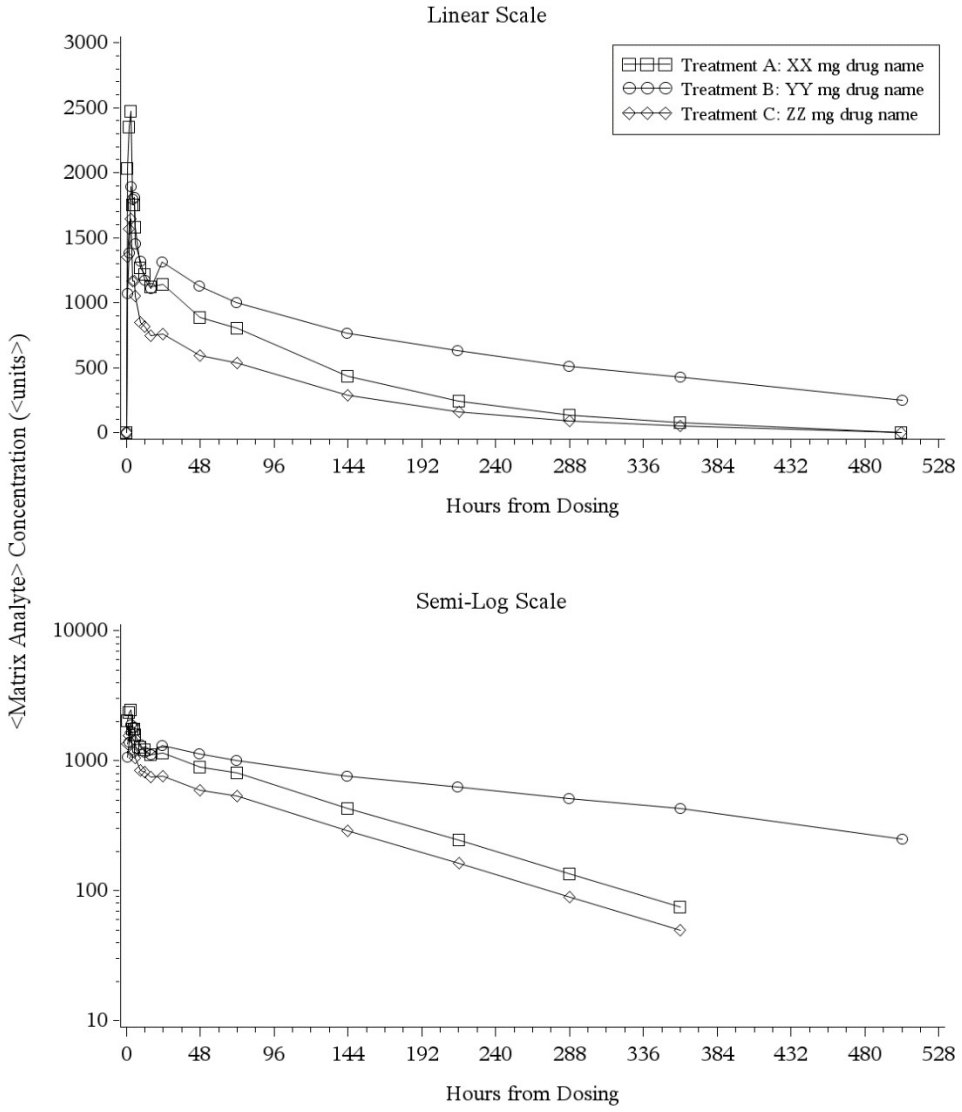


The x-axis title will be: 'Time From Start of Product Use (min)'

Linear and Semi-log Figures in Appendix 16.2.6.1 and 16.2.6.2 will have the following format:

Appendix 16.2.6.1.1

Individual Unadjusted Plasma Nicotine Concentrations Versus Time Following Controlled Product Use (Linear and Semi-Log Scales) (Outcomes Population)



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 4 products 'Time From Start of Product Use (min)' The x-axis title will be: 'Time From Start of Product Use (min)'

15.2 Section 14 Summary Table Shells

Table 14.1.1 Summary of Disposition (Safety Population)

		Randomized Product Sequence				
Category	Product Trial*	XXXX	XXXX	XXXX	XXXX	Overall#
Enrolled	XX	XX	XX	XX	XX	XX
Randomised	XX	XX	XX	XX	XX	XX
Completed	XX	XX	XX	XX	XX	XX
Discontinued Study Early	X	X	X	X	X	X
<Reason1>	X	X	X	X	X	X
<Reason2>	X	X	X	X	X	X
<Reason3>	X	X	X	X	X	X

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Only includes subjects that enrolled in the Product Trial period and dropped prior to randomisation
#Subjects who only participated in the Product Trial period are excluded from the Overall summary.

Program: /CAXXXXX/ sas_prg/stsas/tab cdash_tbldisp1.sas DDMMMYYYY HH:MM

Table 14.1.2 Disposition of Subjects (Safety Population)

Subject Number	Randomised Product Sequence	Product Trial	Product Administered Day 1	Day 2	Day 3	Day 4	Study Completion Status	Da
X	XXXX	Yes	Yes	Yes	Yes	No	Terminated Study Prematurely	DD
X	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
X	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
X	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
X	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
X	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
X	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
X	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
XX	XXXX	Yes	Yes	Yes	Yes	Yes	Completed Study	DD
XX*		Yes	No	No	No	No	Dropped prior to randomisation	DD
XX*		Yes	No	No	No	No	Dropped prior to randomisation	DD
		XX	XX	XX	XX	XX		

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Subject enrolled in the Product Trial period and dropped prior to randomisation.

Program: /CAXXXXX/sas_prg/stsas/tab cdash_tbldisp2.sas DDMMMYYYY HH:MM

Table 14.1.3 Demographic Summary (Safety Population)

Trait		Product Trial*	Randomised Product Sequence				Overall#
			XXXX	XXXX	XXXX	XXXX	
Sex	Male	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	Female	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Race	XXXXXXXXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	XXXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	XXXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Ethnicity	Hispanic or Latino	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	Not Hispanic or Latino	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Age (yrs)	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

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Only includes subjects that enrolled in the Product Trial period and dropped prior to randomisation
#Subjects who only participated in the Product Trial period are excluded from the Overall summary.

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

Programmer Note: Weight (kg), Height (cm), and BMI (kg/m^2) will also be included in the demographic

Table 14.1.4 Smoking History and Usual Brand Attributes Summary (Safety Populatio

Trait		Product Trial*	Randomised Product Sequence XXXX	XXXX	XXXX	XXXX	Overall#
Brand	XXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	XXXXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Brand Style	XXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	XXXXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Flavour	XXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	XXXXXX	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Number of cigarettes Smoked per Day	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
Number of Years Of Smoke Cigarettes	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

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Only includes subjects that enrolled in the Product Trial period and dropped prior to randomisation
#Subjects who only participated in the Product Trial period are excluded from the Overall summary.

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

**Note: Plasma Nicotine Concentration Tables (Tables 14.2.1.1-14.2.1.4 for unadjusted and Tables 14.2.1.5-14.2.1.8 fo
will be in the following format:**

Table 14.2.1.1 Unadjusted Plasma Nicotine Concentrations (ng/mL) Following Controlled Product Use o
Blend stick (Outcomes Population)

Subject Number	Product Sequence	Study Period	Sex	Sample Times (minutes) Pre-use	XX	XX	XX	XX	XX	X
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	X
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	X
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	X
n			Male**	X	X	X	X	X	X	X
Mean				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
CV(%)				XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM				X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
Minimum				XX	XX	XX	XX	XX	XX	X
Median				X.X	X.X	X.X	X.X	X.X	X.X	X.X
Maximum				XX	XX	XX	XX	XX	XX	X

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

Programming Notes: Footnotes to include under the table, as appropriate:
<. = Concentration value missing or not reportable.>
The following footnote will only be included in the unadjusted plasma nicotine tables:
statistics, values that are below the limit of quantitation (BLQ) of <XX> are treated

**There will also be summary statistics for female and overall
The following footnote will only be included in the baseline-adjusted plasma nicotine
adjustment, concentration values that are below the limit of quantitation (BLQ) of <XX
After baseline adjustment, any negative values were assigned a value of zero and all c
is (even if lower than the original limit of quantitation of <xx> ng/mL) for the calcu
For baseline-adjusted table, Pre-use will be replaced with 0.
Concentrations will be presented to same precision as in bio data.
Summary statistics presentation with respect to the precision of the bio data: n = int
+2, Min and Max +0, CV% to 1 decimal.
PK Time points are: pre-use and 2, 4, 6, 8, 10, 15, 30, 45, 60, 120 and 240 minutes fo

Program: /CAXXXXX/sas_prg/pksas/conc-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/conc-tables-sig.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_conc.sas DDMMMYYYY HH:MM

Note: Plasma Nicotine Pharmacokinetic Parameter Tables (Tables 14.2.1.9-14.2.1.12) will be in the following forma

Table 14.2.1.9 Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters) Following Controlle
Intense American Blend stick (Outcomes Population)

				Parameters			
Subject Number	Product Sequence	Study Period	Sex	Parm 1 <unit>	Parm 2 <unit>	Parm 3 <unit>	Parm 4 <unit>
XX	XXXXXX	X	XXXX	X.XX	X.XX	X.XX	X.XX
XX	XXXXXX	X	XXXX	X.XX	X.XX	X.XX	X.XX
XX	XXXXXX	X	XXXX	X.XX	X.XX	X.XX	X.XX
n	Male**			X	X	X	X
Mean				X.X	X.X	X.X	X.X
SD				X.XX	X.XX	X.XX	X.XX
CV(%)				XX.X	XX.X	XX.X	XX.X
SEM				X.XX	X.XX	X.XX	X.XX
Minimum				XX	XX	XX	XX
Median				X.X	X.X	X.X	X.X
Maximum				XX	XX	XX	XX
Geom. Mean				X.X	X.X	X.X	X.X
Geom. CV%				XX.X	XX.X	XX.X	XX.X

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

Programming Note: Footnote to include under the table, as appropriate: <. = Parameter value missing

**There will also be summary statistics for female and overall in the baseline-adjuste
The plasma nicotine PK Parameters are AUC0-90 (ng*min/mL), AUC0-240 (ng*min/mL), AUCt
AUC%extrap (%), Cmax (ng/mL), Clast (ng/mL), Tmax (min), T½ (min), and kel (1/min). Ge
calculated only for Cmax amd AUCs.

Descriptive statistics precision is specified in Section 8.5.

Note: Kel Table 14.2.1.13 will have the following format:

Table 14.2.1.13 Intervals (Minutes) Used for the Determination of Baseline-Adjusted Plasma Nico
(Outcomes Population)

Subject Number	Product	Interval	R2	n
1	A	XX.X - XX.X	X.XXX	X
1	B	XX.X - XX.X	X.XXX	X
1	C	XX.X - XX.X	X.XXX	X
1	D	XX.X - XX.X	X.XXX	X
2	A	XX.X - XX.X	X.XXX	X
2	B	XX.X - XX.X	X.XXX	X
X	X	XX.X - XX.X	X.XXX	X

Product A: < >
Product B: < >
Product C: < >
Product D: < >

Note: R^2 = coefficient of determination of the linear regression
n = Number of points used in kel calculation

Programming Note:

- Interval start and stop times will be presented to 1 decimal or 3 sig figures min;
- R2 will be presented to 3 decimals;
- n will be presented as an integer (with no decimal)

Note: Statistical summary of plasma nicotine PK parameters by product (Table 14.2.1.14) will have the following fo

Table 14.2.1.14 Statistical Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic
AUCt Following Controlled Product Use (Outcomes Population)

Product	Parameter	n	Geometric LS Mean	95% Confide
A	Cmax	x	X.XX	XX.XX - XXX.XX
	AUCt	x	X.XX	XX.XX - XXX.XX
B	Cmax	x	X.XX	XX.XX - XXX.XX
	AUCt	x	X.XX	XX.XX - XXX.XX
C	Cmax	x	X.XX	XX.XX - XXX.XX
	AUCt	x	X.XX	XX.XX - XXX.XX
D	Cmax	x	X.XX	XX.XX - XXX.XX
	AUCt	x	X.XX	XX.XX - XXX.XX

n = Number of observations used in the analysis
Product A: < >
Product B: < >
Product C: < >
Product D: < >
Note: The mixed model includes sequence, product, and study period as fixed effects and s
random effect. Mixed model with a default (variance component) covariance structure
Parameters are ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Me

Program: /CAXXXXX/sas_prg/pksas PROGRAMNAME.SAS DDMMMYYYY HH:MM
Programming note: Geometric LS Means be presented to same precision as Mean in the PK parameter tabl
confidence intervals will be presented to 2 decimal places; p-value will be presented to 4 decimals.

Note: Statistical comparison of PK parameters (Table 14.2.1.15) will have the following format:

Table 14.2.1.15 Statistical Comparison of Baseline-Adjusted Plasma Nicotine Pharmaco
Cmax and AUCs Following Controlled Product Use (Outcomes Population)

Comparison	Parameter	Geometric LS Means Test (n)	Geometric LS Means Reference (n)	% Geometric LS Mean Ratio (Test/Reference)	95
Product A vs Product D	Cmax	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
	AUCt	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
Product B vs Product D	Cmax	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
	AUCt	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
Product C vs Product D	Cmax	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
	AUCt	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
Product A vs Product B	Cmax	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
	AUCt	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
Product A vs Product C	Cmax	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
	AUCt	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
Product B vs Product C	Cmax	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	
	AUCt	X.XX (X)	X.XX (X)	X**XX.XX** - XXX.X	

Test = The first product in the comparison
Reference = The second product in the comparison
n = Number of observation used in the analysis
Product A: < >
Product B: < >
Product C: < >
Product D: < >

The mixed model includes sequence, product, and study period as fixed effects and subje
effect. Mixed model with a default (variance component) covariance structure was used.
Parameters are ln-transformed prior to analysis.
Geometric least-squares means (LS Means) are calculated by exponentiating the LS Means
% Geometric LS Mean Ratio = 100*(Test/Reference)

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

Programming note: Geometric LS Means be presented to same precision as Mean in the PK parameter tabl
confidence intervals will be presented to 2 decimal places; p-value will be presented to 4 decimals.
Include all the comparisons of interested listed in Section 8.6 in the table.

Note: Subjective measure tables for Urge to Smoking VAS Scores (14.2.3.1.1 and 14.2.3.1.2) will have the following

Table 14.2.3.1.1 Summary of Urge to Smoke VAS Scores During and After the Controlled Product Use b
Population)

Product	Sex	Statistics	Product Use Sample Times (minut Pre-use	4	8	15	45	60
A	Male	n	X	X	X	X	X	X
		n missing	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV(%)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Q1	X.X	X.X	X.X	X.X	X.X	X.X
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Q3	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX
		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
	Female	n	X	X	X	X	X	X
		n missing	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV(%)	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Q1	X.X	X.X	X.X	X.X	X.X	X.X
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Q3	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX
		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

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Programmer Note: Summaries for Overall as well as Products B, C, and D (by male, female, overall) will also be include
Difference from preuse table will not have Pre-use column.

Note: Subjective measure tables for Maximum Reduction in Urges to Smoke VAS Scores (14.2.3.1.3) will have the f

Table 14.2.3.1.3 Summary of Urge to Smoke VAS Parameter During and After the Controlled Product Us
Product (Outcomes Population)

Parameter	Sex	Statistics	Product A	Product B	Pro
Emax	Male	n	X	X	
		n missing	X	X	
		Mean	X.X	X.X	
		SD	X.XX	X.XX	
		CV(%)	XX.X	XX.X	
		SEM	X.XX	X.XX	
		Minimum	XX	XX	
		Q1	X.X	X.X	
		Median	X.X	X.X	
		Q3	X.X	X.X	
		Maximum	XX	XX	
		95% CI	X.X-X.X	X.X-X.X	

Product A: < >
Product B: < >
Product C: < >
Product D: < >
Emax = Maximum value of the differences (VASpre-use – VASpost-use)

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

Programming Note: Summaries for Female and Overall will also be included in the table. Parameters include Ema
AUEC0-240.

Note: Statistical summary table of Urges to Smoke Parameters by product (Table 14.2.3.1.4) and Puff Topography 14.2.4.2) will have the following format:

Table 14.2.3.5 Statistical Summary of Urge to Smoke Parameters Emax and AUEC0-240 Follow
Use (Outcomes Population)

Product	Parameter	n	---- LS Mean ------	95% Confidence Interval
A	Emax	X	X.XX	XX.XX - XXX.XX
	AUEC0-240	X	X.XX	XX.XX - XXX.XX
B	Emax	X	X.XX	XX.XX - XXX.XX
	AUEC0-240	X	X.XX	XX.XX - XXX.XX
C	Emax	X	X.XX	XX.XX - XXX.XX
	AUEC0-240	X	X.XX	XX.XX - XXX.XX
D	Emax	X	X.XX	XX.XX - XXX.XX
	AUEC0-240	X	X.XX	XX.XX - XXX.XX

Product A: < >
Product B: < >
Product C: < >
Product D: < >
n = Number of observation used in the analysis
The mixed model includes sequence, product, and study period as fixed effects and subjec
effect. Mixed model with a default (variance component) covariance structure was used.
Least-squares means (LS Means) are calculated from the ANOVA.

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

Programmer Note: Refer to Table 10-2 for the list of topography parameters.

Note: Statistical comparison table of Urges to Smoke Parameters (Table 14.2.3.1.5) and Puff Topography Parameter have the following format:

Tables 14.2.3.1.5 Statistical Comparison of Urge to Smoke Parameters Emax and AUEC0-
(Outcomes Population)

Comparison	Parameter	LS Means Test (n)	LS Means Reference (n)	LS Mean Difference (Test - Reference)
Product A vs Product D	Emax	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
	AUEC0-240	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
Product B vs Product D	Emax	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
	AUEC0-240	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
Product C vs Product D	Emax	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
	AUEC0-240	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
Product A vs Product B	Emax	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
	AUEC0-240	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
Product A vs Product C	Emax	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
	AUEC0-240	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
Product B vs Product C	Emax	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX
	AUEC0-240	X.XX (X)	X.XX (X)	XXX.XXXX.XX - XX

Test = The first product in the comparison
Reference = The second product in the comparison
n = Number of observation used in the analysis
Product A: < >
Product B: < >
Product C: < >
Product D: < >
The mixed model includes sequence, product, and study period as fixed effects and subject-nes
Mixed model with a default (variance component) covariance structure was used.
Least-squares means (LS Means) are calculated from the ANOVA.

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

Programmer Note: Refer to Table 10.2 for the list of topography parameters.

Note: Subjective measure tables for PES factor scores (14.2.3.2) will have the following format.

Table 14.2.3.2 Summary of PES Factor Scores by Study Product for Controlled Product Use (Outc

Subscale	Sex	Statistics	Product A	Product B	P
Satisfaction	Male	n	X	X	
		n missing	X	X	
		Mean	X.X	X.X	
		SD	X.XX	X.XX	
		CV(%)	XX.X	XX.X	
		SEM	X.XX	X.XX	
		Minimum	XX	XX	
		Q1	X.X	X.X	
		Median	X.X	X.X	
		Q3	X.X	X.X	
		Maximum	XX	XX	
		95% CI	X.X-X.X	X.X-X.X	

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Programming Note: Summaries for Female and Overall will also be included in the table. Subscales includes Satisf reward, Aversion, Relief, and single items 17, 19, and 21.

Note: Subjective measure tables for Intent to Use VAS Scores (14.2.3.3.1 through 14.2.3.3.3) will have the following

Table 14.2.3.3.1 Frequency of Responses to Future Intent to Use in Each Category by Study Produc
Product Use (Outcomes Population)

Product	Sex		Use the Product Again Response Category -50 to <0	0	>0 to 50
A	Male	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Female	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Overall	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
B	Male	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Female	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Overall	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
C	Male	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Female	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Overall	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
D	Male	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Female	n (%)	XX(XX%)	XX(XX%)	XX(XX%)
	Overall	n (%)	XX(XX%)	XX(XX%)	XX(XX%)

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Programming Note: The percentage (%) is the row percentage.

Table 14.2.3.3.2 Summary of Future Intent to Use (VAS Score) in Each Category by Study Product for Use (Outcomes Population)

Product	Sex	Statistics	Intent to Use Response Category -50 to <0	>0 to 50
A	Male	n	X	X
		n missing	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		CV(%)	XX.X	XX.X
		SEM	X.XX	X.XX
		Minimum	XX	XX
		Q1	X.X	X.X
		Median	X.X	X.X
		Q3	X.X	X.X
		Maximum	XX	XX
		95% CI	X.X-X.X	X.X-X.X
	Female	n	X	X
		n missing	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		CV(%)	XX.X	XX.X
		SEM	X.XX	X.XX
		Minimum	XX	XX
		Q1	X.X	X.X
		Median	X.X	X.X
		Q3	X.X	X.X
		Maximum	XX	XX
		95% CI	X.X-X.X	X.X-X.X

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Programming Note: Summary for Overall and Products B, C, and D (male, female, and overall) will also be include

Table 14.2.3.3.3 Summary of Future Intent to Use (VAS Raw Scores) by Study Product for Control (Outcomes Population)

Sex	Statistics	Product A	Product B	Product C
Male	n	X	X	X
	n missing	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
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X
Female	n	X	X	X
	n missing	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
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Programmer Note: Overall across male and female will also be included in the table.

Note: Puff topography parameter table (14.2.4.1) will have the following format.

Table 14.2.4.1 Summary of Per-Product Puff Topography Parameters by Study Product and Overall (Ou

Parameter	Sex	Statistics	Product A	Product B
Total Number of Puffs	Male	n	X	X
		n missing	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		CV(%)	XX.X	XX.X
		SEM	X.XX	X.XX
		Minimum	XX	XX
		Q1	X.X	X.X
		Median	X.X	X.X
		Q3	X.X	X.X
		Maximum	XX	XX
		95% CI	X.X-X.X	X.X-X.X
	Female	n	X	X
		n missing	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		CV(%)	XX.X	XX.X
		SEM	X.XX	X.XX
		Minimum	XX	XX
		Q1	X.X	X.X
		Median	X.X	X.X
		Q3	X.X	X.X
		Maximum	XX	XX
		95% CI	X.X-X.X	X.X-X.X

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Programmer Note: Overall across male and female will also be included in the table. Refer to Table 10-2 for the list parameters.

Note: Product use behaviour table (14.2.5.1) will have the following format.

Table 14.2.5.1 Summary of Total Number of HT Sticks Used During the Ad Libitum Product Use
(Safety Population)

Sex	Statistics	Product A	Product B	Product C
Male	n	X	X	X
	n missing	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
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X
Female	n	X	X	X
	n missing	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
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X

Product A: < >
Product B: < >
Product C: < >

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

Programmer Note: Overall across male and female will also be included in the table.

Note: Product use behaviour table (14.2.5.2) will have the following format.

Table 14.2.5.2 Summary of Total Number of CC Smoked on Days -1 through 4 by Smoking Episode (Sa

Sex	Statistics	Day -1	Period 1	Period 2	Period 3
Male	n	X	X	X	X
	n missing	X	X	X	X
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	CV(%)	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Q1	X.X	X.X	X.X	X.X
	Median	X.X	X.X	X.X	X.X
	Q3	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X	X.X-X.X
Female	n	X	X	X	X
	n missing	X	X	X	X
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	CV(%)	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Q1	X.X	X.X	X.X	X.X
	Median	X.X	X.X	X.X	X.X
	Q3	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X	X.X-X.X

Periods 1-4 in the datasets are the days 1-4 in the protocol, respectively.

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

Programmer Note: Overall across male and female will also be included in the table.

Note: Product use behaviour table (14.2.5.3) will have the following format.

Table 14.2.5.3 Summary of Total Number of Puffs During the Controlled Product Use by P
(Safety Population)

Sex	Statistics	Product A	Product B	Product C
Male	n	X	X	X
	n missing	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
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X
Female	n	X	X	X
	n missing	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
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	X.X-X.X	X.X-X.X	X.X-X.X

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Programmer Note: Overall across male and female will also be included in the table.

Table 14.3.1.1 Adverse Event Frequency by Study Product –
Number of Subjects Reporting the Event (% of Subjects Who Received Product) (Safety Popula

		Product				
Adverse Event*	Product Trial#	A	B	C	D	Overall^
Number of Subjects Who Received Study Product	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)
Number of Subjects With Adverse Events	X(X%)	X(XX%)	X(X%)	X(X%)	X(X%)	X(X%)
Number of Subjects Without Adverse Events	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)	XX(XXX%)	XX(XXX%)
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 NOS	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Adverse events are classified according to MedDRA Version 24.1.
#Only include the adverse events that occurred during the product trial period.
The Product Trial period is conducted on Day -1.
^Adverse events that occurred during the product trial period are excluded from Overall summary.

Program: /CAXXXXX/sas_prg/stsas/tab cdash_tblae1a_auto.sas DDMMMYYYY HH:MM

Table 14.3.1.2 Adverse Event Frequency by Product –
Number of Adverse Events (% of Total Adverse Events) (Safety Population)

Adverse Event*	Product Trial#	Product A	Product B	Product C	Product D	Overall^
Number of Adverse Events	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)
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 NOS	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%)

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Adverse events are classified according to MedDRA Version 24.1.
#Only include the adverse events that occurred during the product trial period.
The Product Trial period is conducted on Day -1.
^Adverse events that occurred during the product trial period are excluded from Overall summary.

Program: /CAXXXXX/sas_prg/stsas/tab cdash_tblae1a_auto.sas DDMMMYYYY HH:MM

Table 14.3.1.3 Adverse Event Frequency by Study Product, Severity, and Relationship to
- Number of Subjects Reporting the Event (Safety Population)

Adverse Event*	Product	Number of Subjects With AEs	Severity			Relationship to Product			
			Mild	Moderate	Severe	Unrelated	Unlikely	Possible	Probably
Abdominal pain	X	X	X	X	X	X	X	X	X
Dry throat	X	X	X	X	X	X	X	X	X
Product Trial#		X	X	X	X	X	X	X	X
Study Product A		X	X	X	X	X	X	X	X
Study Product B		X	X	X	X	X	X	X	X
Study Product C		X	X	X	X	X	X	X	X
Study Product D		X	X	X	X	X	X	X	X
Overall^		X	X	X	X	X	X	X	X

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Adverse events are classified according to MedDRA Version 24.1.
#Only include the adverse events that occurred during the product trial period. \
The Product Trial period is conducted on Day -1.
^Adverse events that occurred during the product trial period are excluded from Overall summary.
When a subject experienced the same AE at more than one level of intensity during a product use per
one was counted. When a subject experienced the same AE at more than one level of product relations
period, only the one most closely related to study product was counted.

Program: /CAXXXXX/sas_prg/stsas/tab cdash_tblae4a_auto.sas DDMMMYYYY HH:MM

Table 14.3.1.4 Adverse Event Frequency by Study Product, Severity, and Relationship to
- Number of Adverse Events (Safety Population)

Adverse Event*	Product	Number of AEs	Severity			Relationship to Study Product				L
			Mild	Moderate	Severe	Unrelated	Unlikely	Possible	Probably	
Abdominal pain	X	X	X	X	X	X	X	X	X	
Dry throat	X	X	X	X	X	X	X	X	X	
Product Trial#		X	X	X	X	X	X	X	X	
Study Product A		X	X	X	X	X	X	X	X	
Study Product B		X	X	X	X	X	X	X	X	
Study Product C		X	X	X	X	X	X	X	X	
Study Product D		X	X	X	X	X	X	X	X	
Overall^		X	X	X	X	X	X	X	X	

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*Adverse events are classified according to MedDRA Version 24.1.
#Only include the adverse events that occurred during the product trial period.
The Product Trial period is conducted on Day -1.
^Adverse events that occurred during the product trial period are excluded from Overall summary.

Program: /CAXXXXX/sas_prg/stsas/tab cdash_tblae4a_auto.sas DDMMMYYYY HH:MM

Serious adverse event table (Table 14.3.2.1) will be in the following format.

Table 14.3.2.1 Serious Adverse Events (Safety Population)

There were no serious adverse events recorded during the study

Programmer Note: If there are Serious adverse event follow the shell associated with Appendices 16.2

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

Tables 14.3.4.2 (hematology) and 14.3.4.3, (urinalysis) will resemble 14.3.4.1.

Table 14.3.4.1 Out-of-Range Values and Recheck Results - Serum Chemistry

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Pa
X	XX/X	Screen	.	.	DDMMMYYYY	HH:MM:SS	XX H		
		1	-X	-XX.XX	DDMMMYYYY	HH:MM:SS	XX L	XX L	

F = Female, M = Male
H = Above reference range, L = Below reference range

Programmer Notes: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled as termination chronologically with other scheduled assessments and rechecks. Recheck should be sorted time point the recheck is for. Unscheduled and Early Termination records should only be included if results

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

Tables 14.3.5.3 (hematology) and 14.3.5.5, (urinalysis) will resemble 14.3.5.1.

Table 14.3.5.1 Clinical Laboratory and Change From Baseline Summary - Serum Chemistry (Safety P

Laboratory Test (units)	Reference Range	Time Point	Statistic	Value	Change From B
Testname (unit)	< - >	Day -1	n	X	
			Mean	XX.XX	
			SD	X.XXX	
			Minimum	XX.X	
			Median	XX.XX	
			Maximum	XX.X	
		End of Study	n	X	X
			Mean	X.X	X.X
			SD	X.XX	X.XX
			Minimum	XX	XX
			Median	X.X	X.X
			Maximum	XX	XX

= Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.
breakdown.
Baseline is the last measurement prior to Day 1 product use in the morning.
* Above Reference Range, ^ Below Reference Range

Programmer note: Treatment means at specific time points will be flagged (with a *) if they are abo
normal range. This only applies to the clinical laboratory treatment results (i.e., not the change f
other endpoints).

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

Tables 14.3.5.4 (hematology), and 14.3.5.6 (urinalysis) will resemble 14.3.5.2

P

Table 14.3.5.2 Clinical Laboratory Shift From Baseline - Serum Chemistry (Safety Population)

		Baseline L			Baseline N			Baseline H		
		Post-use			Post-use			Post-use		
Laboratory Test (units)	Time Point	L	N	H	L	N	H	L	N	H
Testname (unit)	End of Study	X	XX	X	X	XX	X	X	XX	X
Testname (unit)	End of Study	X	XX	X	X	XX	X	X	XX	X
Testname (unit)	End of Study	X	XX	X	X	XX	X	X	XX	X

N = Within Reference Range, L = Below Reference Range, H = Above Reference Range
Baseline is the last measurement prior to Day 1 product use in the morning.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programame.sas DDMMMYYYY HH:MM

For urinalysis, the following footnote is used since the categories of N and O will be used instead
Note: N = Within Reference Range, O = Outside Reference Range.

Table 14.3.5.7 Vital Sign and Change From Baseline Summary (Safety Population)

Vital Sign (units)	Time Point	Statistic	Value	Change From Basel
Testname (unit)	Day -1	n	X	
		Mean	XX.XX	
		SD	X.XXX	
		Minimum	XX.X	
		Median	XX.XX	
		Maximum	XX.X	
	Day 1 Preuse	n	X	
		Mean	X.X	
		SD	X.XX	
		Minimum	XX	
		Median	X.X	
		Maximum	XX	
	Day 2 Preuse	n	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		Minimum	XX	XX
		Median	X.X	X.X
		Maximum	XX	XX

Baseline is the last measurement prior to Day 1 product use in the morning.

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

Table 14.3.5.8 12-Lead Electrocardiogram and Change From Baseline Summary (Safety Populati

Measurement (units)	Time Point	Statistic	Value	Change From Baseline
Testname (unit)	Day -1	n	X	
		Mean	XX.XX	
		SD	X.XXX	
		Minimum	XX.X	
		Median	XX.XX	
		Maximum	XX.X	
	End of Study	n	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		Minimum	XX	XX
		Median	X.X	X.X
		Maximum	XX	XX

Baseline is the last measurement prior to Day 1 product use in the morning.

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

Table 14.3.5.9 Incedence of Device Malfunction by Product (Safety Population)

Device Malfunction	Product Trial#	Product A	Product B	Product C	Product D
Number of Subjects Who Used the Device	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)
Number of Subjects Experienced Device Malfunction	X(X%)	X(XX%)	X(X%)	X(X%)	X(X%)
Event description 1	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
Event description 2	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
Event description 3	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)

Product A: < >
Product B: < >
Product C: < >
Product D: < >
#Only include the adverse events that occurred during the product trial period.
The Product Trial period is conducted on Day -1.

Program: /CAXXXXX/sas_prg/stsas/tab cdash_tblae1a_auto.sas DDMMMYYYY HH:MM

16. 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. These listings will be generated off of the Celerion SDTM Tabulation Model 1.4 mapped in accordance with SDTM Implementation Guide 3.2. All listings will be presented in Courier New font size 9.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Reference
Serum Chemistry	Testname1	MALE		XX - X
	Testname2	MALE	0-25	XX - X
			26-99	XX - X
	<similar for all other tests note that age will only be presen			
Hematology	<similar to serum chemistry>			
Urinalysis	Testname	MALE		NEGATI
	Amphetamines	MALE		NOT DE

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

Appendix 16.2.1 Subject Disposition (Safety Popul

Subject Number	Randomisation Sequence	Actual Sequence	Study Period	End of Product Date	End of Product Completed Product?	End of Product Reason for Discontinuation pecify	End of Product Date
1	XXXX	XXXX	Post	DDMONYYYY	YES		DDMONYYYY
2	XXXX	XXXX	Post	DDMONYYYY	YES		DDMONYYYY
3	XXXX	XXX	Post	DDMONYYYY	NO	Adverse Event	DDMONYYYY

Product A: Pulze HT device with iD Intense American Blend stick
Product B: Pulze HT device with iD Regular American Blend stick
Product C: Pulze HT device with iD Regular Menthol stick
Product D: Subject's own brand combustible cigarette (OBCC)

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

Appendix 16.2.4.1 Demographics (Safety Popula

Subject Number	Year Of Birth	Age (yr)	Sex	Race	Ethnicity	Height (cm)	We (k
1	YYYY	47	Male	< >	Not Hispanic or Latino	XXX	XX.
2	<similar to above.						

Age is approximated as year of informed consent – year of birth. There will be an addition of 1 if t
the age specified in the inclusion criteria or a subtraction of 1 if the difference in years is 1 mo
inclusion criteria.

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

Appendix 16.2.4.2 Oral/Physical Examination (I of II) (Safety Populati

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

HEENT = Head, eyes, ears, nose, throat

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

Appendix 16.2.4.3 Oral/Physical Examination (II of II) (Safety Populati

Subject Number	Study Period	Date	System7	System8	System9	System10	System11	Syst
X	Screen	DDMMMYYYY	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORM
X	Screen	DDMMMYYYY	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORM
X	Screen	DDMMMYYYY	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORM

HEENT = Head, eyes, ears, nose, throat

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

Appendix 16.2.4.4 Medical History (Safety Population)

Subject Number	Any History?	Condition or Event	Date		
			Start	End	Ongoing?
1	No				
2	Yes	< >	YYYY		YES
			<note date can be YYYY, MONYYYY, or DDMONYYYY bas		

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

Appendix 16.2.4.5 Smoking History and Usual Brand Attributes (Safety Popul

Subject Number	Substance	Start Date	End Date	Amount	Brand	Brand Style
1	Tobacco Use	DDMONYYYY		XXXXXXXX	XXXXX	XXXXXXXXX

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

Appendix 16.2.5.1 Subject Eligibility (Safety Po

Subject Number	Study Period	Did subject meet all eligibility criteria?	Criterio Not Met
1	Screen	YES	
2	Screen	NO	Exclusi

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

Appendix 16.2.5.2 Product Trial (Safety Population)

Subject Number	Study Period	Day	Hour	Start Date	Start Time	Stop Date	Stop Time
1	Check-in	-1	-17.75	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS

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

Appendix 16.2.5.3 Product Descriptions

Product	Test Material Name	Route	Form
X	XXXXXXXXXXXX	INHALATION	HEATED TOBACCO PRODUCT

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

Appendix 16.2.5.4 Product Use (Safety Population)

Subject Number	Study Period	Product	Day	Interval	Start Date	Start Time	Stop Time	Puff Count
1	1	X	1	0.00 TO 0.10	DDMONYYYY	HH:MM:SS	HH:MM:SS	XX
				4.03 TO 8.03	DDMONYYYY	HH:MM:SS	HH:MM:SS	

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Appendix 16.2.5.5 Ad Lib Smoking (Safety Population)

Subject Number	Study Period	Product	Day	Hour	Start Date	Start Time	Stop Date	Stop Time
1	1	X	1	X.XX	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS
				X.XX	DDMONYYYY	HH:MM:SS	DDMONYYYY	HH:MM:SS

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Appendix 16.2.5.6 Prior and Concomitant Medications (Safety

Subject Number	Product	Prior?	Medication (WHO DD)	Dosage	Route	Start Date	Start Time	End Date	End Time
1			None						
2			None						
3		Yes	CETIRIZINE (CETIRIZINE)	X MG	BY MOUTH	DDMONYYYY		DDMONYYYY	HH:MM
	B	No	PARACETAMOL (PARACETAMOL)	X MG	XXXXXXXXX	DDMONYYYY	HH:MM	XXXXXXXXX	HH:MM

Product A: < >
Product B: < >
Product C: < >
Product D: < >
Concomitant medications are coded with WHO Drug Dictionary Version 01SEP2021 b3.
WHO DD = World Health Organization Drug Dictionary

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

Appendix 16.2.5.7 Plasma Nicotine Pharmacokinetic Blood Draw Times and Concentration D

Subject Number	Study Period	Product	CRF Day	CRF Hour	Blood Draw Date	Blood Draw Time	Elapsed Time From Last Product Use (Hour)	Unadju Conce (unit
1	1	A	1	-0.05	DDMONYYYY	HH:MM:SS	0.0	X.XX
				0.25	DDMONYYYY	HH:MM:SS	0.265	X.XX
				0.50	DDMONYYYY	HH:MM:SS	0.590	X.XX
			< >					

<similar for all other time points and subjects>

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

- Population: Safety population will be used in this listing.
- Time may be expressed in minutes, as appropriate.

Appendix 16.2.6.3 Urge to Smoke (Safety Population)

Subject Number	Study Period	Product	Day	Hour	Date	Was Event Performed?	Score	Comm
1	1	X	1	X.XX	DDMONYYYY	XXX	XX	
				X.XX	DDMONYYYY	XXX	XX	
				X.XX	DDMONYYYY	XXX	XX	
				X.XX	DDMONYYYY	XXX	XX	

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Appendix 16.2.6.4 Urge to Smoke Parameters (Safety Population)

Subject Number	Study Period	Product	Day	Date	Emax	TEmax	AU
1	1	X	X	DDMONYYYY	XXX	XX	
	2	X	X	DDMONYYYY	XXX	XX	
	3	X	X	DDMONYYYY	XXX	XX	

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Appendix 16.2.6.5 Product Evaluation Scale Collection (Safety Populatio

Subject Number	Study Period	Product	Date	Time	Was Event Performed?	Comments
1	1	X	DDMONYYYY	HH:MM	XXX	
	2	X	DDMONYYYY	HH:MM	XXX	

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Appendix 16.2.6.6 Product Evaluation Scale Item Score (Safety Populatio

Subject Number	Study Period	Product	Date	Time	Question 1	2	3	4	5	6	7	8
1	1	X	DDMONYYYY	HH:MM	X	X	X	X	X	X	X	X
	2	X	DDMONYYYY	HH:MM	X	X	X	X	X	X	X	X

Product A: < >
Product B: < >
Product C: < >
Product D: < >
1. Was it satisfying? 2. Did it taste good? 3. Did you enjoy the sensations in your mouth? 4. Did
5. Did it make you feel more awake? 6. Did it make you feel less irritable? 7. Did it help you con
8. Did it reduce your hunger for food? 9. Did it make you dizzy? 10. Did it make you nauseous?
11. Did it immediately relieve your craving for a cigarette? 12. Did you enjoy it? 13. Did it reli
14. Did it relieve the urge to smoke? 15. Was it enough nicotine? 16. Was it too much nicotine? 1
18. Were there bothersome side effects? 19. Were you comfortable using the product in public?
20. Did you still have a craving for a cigarette after using the product?
21. Are you concerned that you would become dependent on this product?
Scale: 1 = not at all; 2 = very little; 3 = a little; 4 = moderately; 5 = a lot; 6 = quite a lot; 7

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

Appendix 16.2.6.7 Product Evaluation Scale Factor Score (Safety Populati

Subject Number	Study Period	Product	Date	Time	Factor: Satisfaction	Factor: Psychological Reward	Factor: Relief	Factor: Aversion	Factor: Use	Factor: in
1	1	X	DDMONYYYY	HH:MM:SS	X	X	X	X		
	2	X	DDMONYYYY	HH:MM:SS	X	X	X	X		

Product A: < >
Product B: < >
Product C: < >
Product D: < >
Factor score: Satisfaction: Average of items 1, 2, 3, and 12; Psychological Reward: Average of item
Aversion: Average of items 9, 10, 16, and 18; Relief: Average of items 11, 13, 14, 15, and reversed
Easy to Use: Single item 17; Comfortable in public: Single item 19; Concern for become dependent: Si
Refer to Appendix 16.2.6.6 for description of questions.

Scale: 1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = a lot, 6 = quite a lot, 7

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

Appendix 16.2.6.7 Intent to Use (Safety Population)

Subject Number	Study Period	Product	Date	Time	Was Event Performed?	VAS Score*
1	1	X	DDMONYYYY	HH:MM	XXX	XX

Product A: < >
Product B: < >
Product C: < >
Product D: < >
*If available, how likely are you to buy your assigned study product in the future?
Scale: 0 = not at all; 100 = extremely

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

Appendix 16.2.6.9 Puff Topography Parameters – Per-Puff (Safety Populati

Subject Number	Study Period	Product	Date	Time	Was Event Performed?	Puff Count	Puff Duration (s)	Puff Volume (mL)	Peak Pu Flow Ra (mL/s)
1	X	X	DDMONYYYY	HH:MMM	X	X	XX	XX	XX
						X	XX	XX	XX
						X	XX	XX	XX
						X	XX	XX	XX

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Appendix 16.2.6.9 Puff Topography Parameters – Per-Product Use (Safety Population)

Subject Number	Study Period	Product	Total Puff Number	Total Puff Volume (mL)	Average Puff Volume (mL)	Total Puff Duration (s)	Average Puff Duration (s)	Average Flow Rate (mL/s)	Avera Flow (mL
X	X	X	X	XX	XX	XX	XX	XX	X
	X	X	X	XX	XX	XX	XX	XX	X
X	X	X	X	XX	XX	XX	XX	XX	X
	X	X	X	XX	XX	XX	XX	XX	X

Product A: < >
Product B: < >
Product C: < >
Product D: < >

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

Appendix 16.2.6.10 Product Use Behaviour (Safety Population)

Subject Number	Study Period	Product	Interval	Number of HT Sticks Used	Number of CC Smokerd	Number of Puffs
1	X	X	0.00 TO 0.10	X	X	XX
			4.03 TO 8.03	XX	XX	
	X	X	0.00 TO 0.10	X	X	XX
			4.03 TO 8.03	XX	XX	
	X	X	0.00 TO 0.10	X	X	XX
			4.03 TO 8.03	XX	XX	
	X	X	0.00 TO 0.10	X	X	XX
			4.03 TO 8.03	XX	XX	

Product A: < >
Product B: < >
Product C: < >
Product D: < >
HT = Heated tobacco; CC = Combustible cigarette

Program: /CAXXXXX/sas_prg/stsas/lis/programname.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 Product Use (DD:HH:MM)	Date:Time Start/ Stop Duration (DD:HH:MM)	Serious/ Outcome	Sever Frequ
1	30/F			None				
2	24/M			None				
3	52/M	A	Yes	XXXXXXXXXXXX/ XXXXXXXXXXXXXXXX (XXXXXXXXXXX)	XX:XX:XX	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15	No/ Recovered/ Resolved	Moder Inter
		B	Yes	<similar to above>				

Product A: < >
Product B: < >
Product C: < >
Product D: < >
Adverse events are classified according to MedDRA Version 24.1.
PUE = Abbreviation for product-use-emergent
F = Female; M = Male

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

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

Appendix 16.2.7.2 Details for Serious Adverse Events (Safet

Subject Number	Age/ Sex	Product	PUE?	System Organ Class/ Preferred Term (Verbatim)	Date:Time Start/ Stop Duration (DD:HH:MM)	Serious Event?	Death	Life-Threat?	Hospital-ization?
1	30/F			None					
2	24/M			None					
3	52/M	A	Yes	XXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX (XXXXXXXXXXX)	DDMONYYYY:HH:MM/ DDMONYYYY:HH:MM 00:23:15	Yes	No	No	Yes

Product A: < >
Product B: < >
Product C: < >
Product D: < >
Adverse events are classified according to MedDRA Version 24.1.
PUE = Abbreviation for product-use-emergent
F = Female; M = Male

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

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

Appendix 16.2.7.3 Device Malfunction (Safety Population)

Subject Number	Age/ Sex	Study Period	Product	Did the Device Malfunction?	Date	Time	Device Serial Number	Comment
1	30/F	X	X	XXX	DDMMMYYYY	HH:MM	XXXXXXXXXX	XXXXXX

Product A: < >
Product B: < >
Product C: < >
Product D: < >
F = Female; M = Male

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

Appendices 16.2.8.2 – 16.2.8.4 will resemble 16.2.8.1.

Appendix 16.2.8.1 Clinical Laboratory Report - Serum Chemistry (Safety Populat

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Chloride M: 97-105 (mEq/L)	Potassium M: 3.7-5.2 (mEq/L)
1	XX/M	Screen			DDMONYYYY	HH:MM:SS	XXX	X.X
		Check-in	-1	-22.50	DDMONYYYY	HH:MM:SS	XXX H	X.X
		Recheck			DDMONYYYY	HH:MM:SS	XXX	X.X
		4	1	8.67	DDMONYYYY	HH:MM:SS	XXX	X.X
<similar to above for all subjects/time points>								

F = Female; M = Male
H = Above reference range

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

Appendix 16.2.8.5 Carbon Monoxide Breath Test (Safety Popul

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Result (ppm)	Comm
1	30/F	Screen			DDMMMYYYY	HH:MM:SS	XX	
		Check-in	-1	-XX.X	DDMMMYYYY	HH:MM:SS	XX	

F = Female; M = Male

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

Appendix 16.2.8.6 Vital Signs (Safety Population)

Subject Number	Age/ Sex	Study Period	Product	Day	Hour	Date	Time	Blood Pressure (mm Hg) Systolid/Diastolic
1	30/F	Screen				DDMONYYYY	HH:MM:SS	XXX/ XX
						R	HH:MM:SS	XXX/ XX
						R	HH:MM:SS	XXX/ XX
		1	A	-1	-17.0	DDMONYYYY	HH:MM:SS	XXX/ XX

Product A: < >
Product B: < >
Product C: < >
Product D: < >
F = Female; M = Male
R = Recheck value; brpm = breaths/min

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

Appendix 16.2.8.7 12-Lead Electrocardiogram (Safety Populati

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Result	Heart Rate (bpm)	RR (msec)	PR (msec)	QRS (msec)	QT (msec)	QTcF (msec)
1	30/F	Screen			DDMONYYYY	X:XX:XX	WNL	XX	XXX	XX	XX	XXX	XXX
		1	-X	X.XX	DDMONYYYY	XX:XX:XX	ANCS	XX	XXX	XX	XX	XXX	411
			X	X.XX R	DDMONYYYY	XX:XX:XX	< >	XX	XXX	XX	XX	XXX	451#

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
# = QTc value greater than 450 msec; @ = QTc change from baseline greater than 30 msec

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