Statistical Analysis Plan

A Single-Center, Open-Label, Concentration-Ranging Study to Investigate the Nicotine Pharmacokinetic Profiles and Pharmacodynamic Effects of the P4M3 Variants in Relation to Subjects' Own Electronic Cigarettes in Healthy, Adult Experienced Users of Electronic Cigarettes

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Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Celerion
[redacted]

Statistical Analysis Plan Signature Page

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Signature [redacted] Date: 30 Nov 2017

Steffen Fredersdorf, PhD [redacted]
Clinical Scientist
Philip Morris Products S.A., Neuchâtel, Switzerland

Signature: [redacted] Date: 30 Nov 2017

[redacted] MD
Medical Safety Officer
Philip Morris Products S.A., Neuchâtel, Switzerland

Signature: [redacted] Date: 30 NOV 2017

Study Biostatistician
Philip Morris Products S.A., Neuchâtel, Switzerland

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Signature: [redacted] Date: 30 NOV 2017

Senior Biostatistician II, Data Management and Biometrics
Celerion, [redacted]

Signature [redacted] Date: 30-NOV-2017

Pharmacokinetic Scientist, Clinical Pharmacology and Pharmacometrics,
Data Management and Biometrics
Celerion, [redacted]

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LIST OF ABBREVIATIONS AND EXPLANATION OF TERMS

Abbreviations

Adapted mCEQ	Adapted version of the modified Cigarette Evaluation Questionnaire
AE(s)	Adverse event(s)
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the concentration time curve
$AUC_{(0\text{-}4h)}$	Area under the concentration-time curve from T0 to 4 hours in fixed regimen
BMI	Body mass index
$cAUC_{(0\text{-}4h)}$	Background-corrected area under the concentration-time curve from T0 to 4 hours [*ad libitum* use and fixed regimen]
$AUCb_{(0\text{-}4h)}$	Area under the concentration-time curve that is above the corrected baseline from T0 to 4 hours during the *ad libitum* use
CC(s)	Conventional cigarette(s)
$cC_{average}$	Background-corrected average of plasma nicotine concentrations between T0 and 1 hour during *ad libitum* use
cC_{max}	Background-corrected maximum plasma nicotine concentration during fixed regimen
cC_{peak}	Background-corrected peak plasma nicotine concentration during *ad libitum* use
cC_{trough}	Background-corrected trough plasma nicotine concentration during *ad libitum* use
CI	Confidence interval
$C_{average}$	Average of plasma nicotine concentrations between T0 and 1 hour during *ad libitum* use
C_{max}	Maximum plasma nicotine concentration during fixed regimen
C_{peak}	Peak plasma nicotine concentration during *ad libitum* use
C_{trough}	Lowest plasma concentration after T0 during *ad libitum* use
CO	Carbon monoxide
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CV (%)	Coefficient of variation (%)

CV (documentation)	Curriculum vitae
CYP2A6	Cytochrome P450 2A6
e-cigarette	Electronic cigarette
ECG	Electrocardiogram
EOS	End of Study
EU	European Union
FDA	US Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
HIV	Human immunodeficiency virus
HPT	Human puffing topography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IP	Investigational Product
LA	Lactic acid
LLOQ	Lowest limit of quantification
LS	Least-squares
mg	milligram
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
ms	Millisecond
n	Number of subjects
ng	Nanogram
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMI	Philip Morris International
PPM	Parts per million
QTcB	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, using Bazett's formula
QTcF	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Standard deviation
SQ	Sensory questionnaire
T	Time point
T0	Time point of first product use during study day
$t_{½}$	Half-life
t_{max}	Time to maximum concentration during fixed regimen
t_{peak}	Time to peak plasma nicotine concentration during *ad libitum* use
UBC	United BioSource Corporation
VAS	Visual Analogue Scale
WBC	White blood cell (count)
WHO	World Health Organization
µg	Microgram

Explanation of Terms

The following special terms are used in this protocol:

CC	The term 'cigarette' refers to manufactured and commercially available cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
Early Termination	Enrolled subject(s) who withdraw or is/are discontinued from the study on Day 5 (prior to completion of scheduled study procedures) or earlier. Subjects who are discontinued from the study will have early termination procedures performed at discontinuation.
End of Study	End of Study for a subject is defined as the last day of the 7-day passive safety FU subsequent to discharge from the unit.
Enrollment	On Day -2 for eligible subjects, after all applicable inclusion and exclusion criteria have been satisfactorily assessed and the subjects are willing and ready to use P4M3.
First product use time point	Start of product use for P4M3 is defined as the time of the first puff.
Passive safety FU	After the time of discharge, a 7-day passive safety FU will be conducted for the recording of spontaneously reported (by subject) new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the Investigator. In general, any AE will be followed up until resolved, stabilized i.e., no worsening of the event or a plausible explanation for the event has been found.
Screen failure	Subjects who do not meet the entry criteria from ICF signature to the time of enrollment.
Time of Discharge	Time when the subject is released from the investigational site after all the procedures of the day of discharge have been conducted.

1. INTRODUCTION

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

Any additional analyses not addressed within this SAP and/or driven by the data, or requested by Philip Morris Products S.A., will be considered out of scope and must be described in the study report.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoints

1. To evaluate the plasma concentration-time profile of nicotine and derived pharmacokinetic (PK) parameters of the P4M3 variants with subjects' own electronic cigarette (e-cigarette) from the 60 minutes *ad libitum* use.

Endpoints:

- Total and background-corrected plasma nicotine concentration *versus* time profiles
- Background-corrected peak plasma nicotine concentration [cC_{peak}]
- Time to peak plasma nicotine concentration [t_{peak}]
- Background-corrected trough plasma nicotine concentration [cC_{trough}]
- Background-corrected average of plasma nicotine concentration between 0 to 1 hour [$cC_{average}$]
- Background-corrected area under the concentration-time curve that is above the corrected baseline from the start of product use to 4 hours [$cAUC_{(0\text{-}4h)}$]

2.2 Secondary Objectives and Endpoints

1. To evaluate the plasma concentration-time profile of nicotine and derived PK parameters of the P4M3 variants with subjects' own e-cigarette from the fixed puffing regimen.

Endpoints:

- Total and background-corrected plasma nicotine concentration versus time profiles
- Background-corrected maximum plasma concentration [cC_{max}]
- Time to the maximum concentration [t_{max}]
- Background-corrected area under the concentration-time curve that is above the corrected baseline from the start of product use to 4 hours [$cAUC_{(0-4h)}$]

2. To evaluate pharmacodynamic (PD) effects (subjective effects and related behavioral assessments) of the P4M3 variants and subjects' own e-cigarette.

Endpoints:

- Product evaluation by an adapted version of the modified Cigarette Evaluation Questionnaire (Adapted mCEQ) (60 minutes *ad libitum* use only)
- Visual Analogue Scale (VAS) for craving (fixed puffing and 60 minutes *ad libitum* use)
- Adapted Sensory Questionnaire (SQ) (fixed puffing and 60 minutes *ad libitum* use)

3. To evaluate human puffing topography (HPT) of the P4M3 variants and the subjects' own e-cigarette from the fixed puffing regimen and the 60 minutes *ad libitum* use.

Endpoint:

- Per-Puff parameters and Per-Product use experience parameters (see Appendix 1 in Protocol)

4. To evaluate the association between theoretical nicotine exposure and PK parameters of the P4M3 variants from the 60 minutes *ad libitum* use and the fixed puffing regimen.

Endpoints:

- Theoretical nicotine exposure calculated as total puff volume [mL] (from HPT) x nicotine [µg/mL] (deriving the nicotine [µg/mL] from the CORESTA [Cooperation Centre for Scientific Research Relative to Tobacco] regimen to determine the nicotine [µg] per puff [55 mL]) for each of the P4M3 variants.
- cC_{peak} versus theoretical rate of nicotine inhalation (R_0) (60 minutes *ad libitum* use only)

- $cAUC_{(0\text{-}4h)}$ versus theoretical nicotine exposure (60 minutes *ad libitum* use only)
- cC_{max} versus theoretical rate of nicotine inhalation (R_0) (fixed puffing regimen only)
- $cAUC_{(0\text{-}4h)}$ versus theoretical nicotine exposure (fixed puffing regimen only)

5. To evaluate the association between PK parameters and HPT parameters of the P4M3 variants from the 60 minutes *ad libitum* use and the fixed puffing regimen.

Endpoints:

- HPT parameters: total puff volume, average flow, average puff duration, average puff volume
- $cC_{average}$ (60 minutes *ad libitum* use only)
- $cAUC_{(0\text{-}4h)}$ versus HPT parameters (60 minutes *ad libitum* use only)
- cC_{peak} versus HPT parameters (60 minutes *ad libitum* use only)
- cC_{max} versus HPT parameters (fixed puffing regimen only)
- $cAUC_{(0\text{-}4h)}$ versus HPT parameters (fixed puffing regimen only)

6. To assess amount of e-liquid use of the P4M3 variants following the 60 minutes *ad libitum* use and the fixed puffing regimen.

Endpoint:

- Weight difference of cartridge before and after each product use regimen

7. To monitor the safety and tolerability during the study.

Endpoints:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Frequency of AEs and SAEs
- Incidence of P4M3 device events including malfunction/misuse
- Physical examination changes from baseline
- Changes from baseline of VAS, three Likert scales and the open question of Cough assessment questionnaire

- Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, QTcB , QTcF intervals)
- Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Spirometry changes from baseline (forced expiratory volume in 1 second [FEV_1], FEV_1 % predicted, forced vital capacity [FVC], FEV_1/FVC)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel
- Concomitant medications

Note: Celerion Biometrics will only addresses Secondary Objectives 2, 3, 4, 5, 6 and 7.

3. STUDY DESIGN

This is a single-center, open–label, concentration-ranging study to evaluate the nicotine PK profile and PD effects in healthy white adult experienced users of closed tank/cartridge e-cigarettes using four different variants of P4M3 (nicotine concentration of 1.7%, 1.7% with 1.1% lactic acid [LA], 3% with 1.1% LA, and 4% with 2% LA) or their own e-cigarettes.

A Screening Visit, including a demonstration of the P4M3 by the investigational site personnel, will be conducted within 3 weeks (Day -23 to Day -3) prior to Admission (Day -2) (see Figure 1).

On Day -2, subjects will be admitted to the investigational site at Admission. Subjects should have been fasting for at least 12 hours prior to Admission. After confirmation of subjects' eligibility, subjects will be enrolled in the study and have a debriefing on P4M3 followed by a product test with P4M3-1.7% *ad libitum* for a maximum of 10 minutes. After the product test, subjects not willing and/or not ready to use (e.g., intolerance) P4M3 will be discontinued and may be replaced. Subjects willing to continue will enter their confinement period of 6 days, from Day -2 to Day 5. Following the product test, subjects will be required to abstain from any nicotine/tobacco containing product use for at least 10 hours until the first product use on Day -1.

On Day -1 to Day 4, subjects will use either their own closed tank/cartridge e-cigarette/e-liquid or one P4M3 variant with two different regimens as described in Figure 1:

- a fixed puffing regimen comprising of 12 puffs in total at a rate of one puff every 30 seconds (± 5 seconds) with HPT recording in the morning.

- *ad libitum* use for 60 minutes (± 5 minutes) with HPT recording in the afternoon

The start of product use of subjects' own e-cigarette and P4M3 variant (first puff) for fixed puffing and for the 60 minutes (± 5 minutes) *ad libitum* use will be defined as T0. T0 should be at approximately the same time (± 30 minutes) for fixed puffing in the morning and for *ad libitum* use in the afternoon for subjects' own e-cigarette on Day -1 (Baseline) and for P4M3 variants on Days 1 to 4. T0 for 60 minutes *ad libitum* use should be at least 10 hours after T0 for fixed puffing. There will be a washout of at least 10 hours following each *ad libitum* product use with respect to the subsequent fixed puffing regimen in the next morning to allow adequate background correction of the fixed puffing regimen-related plasma nicotine concentrations.

On Day -1 (Baseline), subjects will be instructed to use their own closed tank/cartridge e-cigarette with fixed puffing in the morning and subsequently, to use it *ad libitum* for 60 minutes in the afternoon (Figure 1).

On Day 1, subjects will be randomized to one of two sequences of the P4M3 variants in order to crossover the use of P4M3-1.7% and P4M3-1.7%LA:

Sequence 1:

P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA

Sequence 2:

P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA

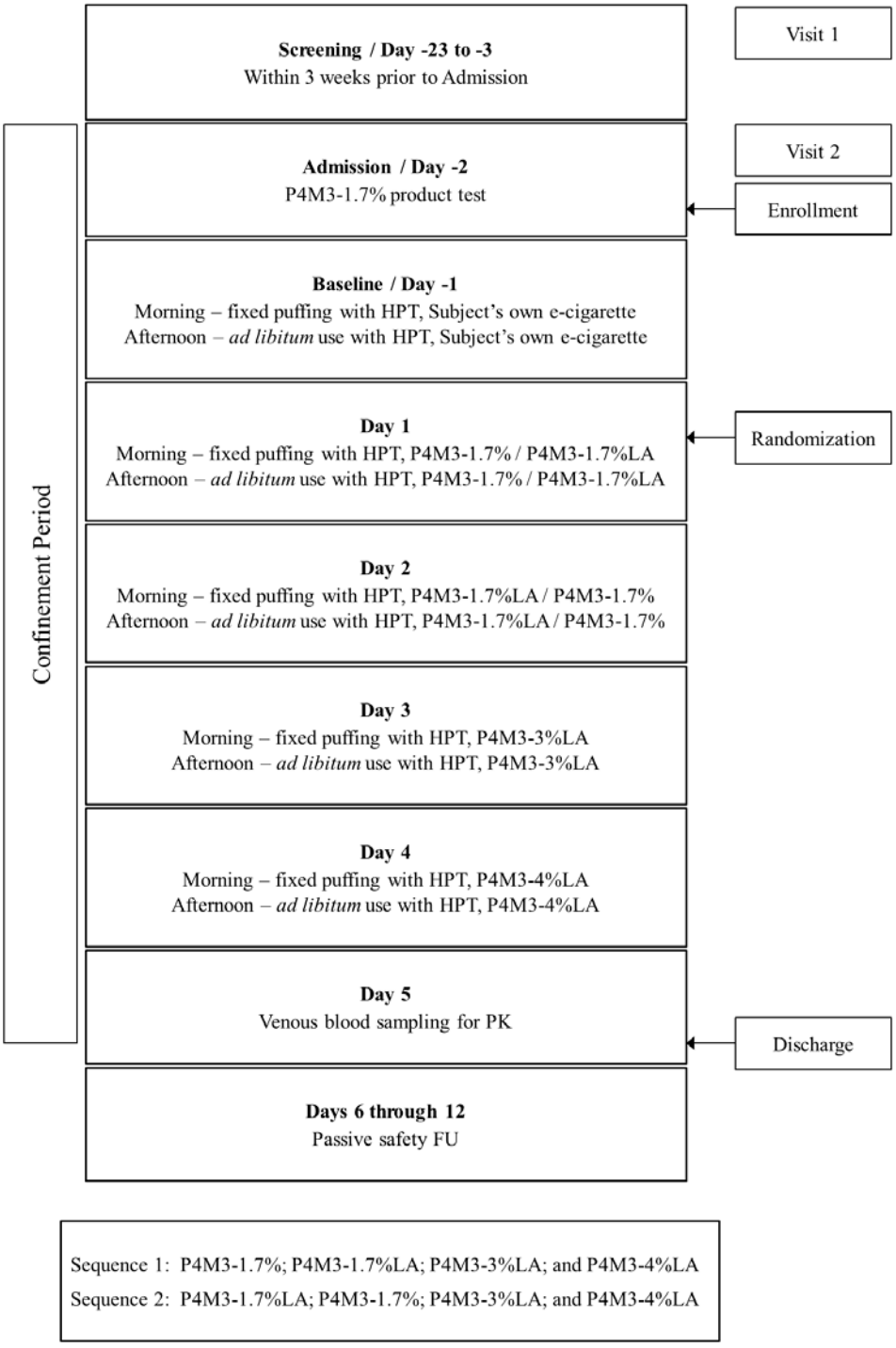
On Days 1 to 4, subjects will be provided and instructed to use a new, ready-to-use product (full cartridge) of the assigned P4M3 variant for fixed puffing regimen with HPT recording in the morning and another new one for the *ad libitum* use for 60 minutes with HPT recording in the afternoon, according to one of two randomly assigned sequences. The concentration of P4M3 e-liquid will be the same on a given day for fixed puffing and *ad libitum* use on Days 1 to 4. During confinement, the use of nicotine/tobacco containing products other than the one allocated during the scheduled use periods will not be allowed.

Venous blood samples will be taken for analysis of PK parameters prior to the start of and during both fixed puffing and the 60 minutes *ad libitum* use at specified time points before and after T0 on Day -1 to Day 4. Blood sampling for the determination of nicotine and derived PK parameters will be collected for 4 hours following T0 of fixed puffing in the mornings and for 4 hours following T0 of *ad libitum* use in the afternoons.

On Day 5, subjects will remain in the study center for additional PK blood sampling up to 24 hours after T0 of the *ad libitum* use on Day 4 for the purposes of estimating the terminal elimination half-life.

Subjects will be discharged following completion of assessments at Day 5 and will enter a 7-day passive safety follow-up (passive safety FU) during which there will be recording of spontaneously reported new AE/SAEs and the active follow-up of ongoing AE/SAEs by the Investigator. Any non-serious AE that is ongoing during the passive safety FU will be actively followed up by the Investigator or designee during that period until it has been resolved, stabilized (i.e., no worsening of the condition), an acceptable explanation has been found (e.g., a chronic condition) or lost to follow-up. At the end of the passive safety FU, all ongoing non-serious AEs will be documented as "ongoing" and no additional follow-up information will be sought by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly. All SAEs will be followed up by the Investigator or designee, despite their continuation after the end of the passive safety FU, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). SAEs reported after the subject's end of study (EOS) that are considered related to the PMI investigational product (IP) by the Investigator must be captured and reported to United BioSource Corporation (UBC)/PMI regardless of time after EOS. The EOS for a subject is defined as his/her discharge on Day 5 or the date of early termination of the subject, plus 7 days of passive safety FU.

Figure 1 Study Schematic



4. SAMPLE SIZE ESTIMATION

The sample size is empirically based, as there is no prior information on which to base the sample size and there is no consideration for statistical hypothesis. A sample of 12 subjects is targeted for the analysis of this study to optimize the precision about the mean and variance for the study objectives. Therefore, 16 subjects will be randomized to allow for up to 25% of subjects to have at least one product exposure period with incomplete data.

5. SUBJECT RANDOMIZATION

The randomization scheme will be generated at Celerion by a biostatistician using a computerized program.

Subjects will be randomized to either one of two sequences of IP exposures:

Sequence 1:

P4M3-1.7%; P4M3-1.7%LA; P4M3-3 %LA; and P4M3-4%LA

Sequence 2:

P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA

6. ANALYSIS POPULATIONS

6.1 Analysis Populations

Pharmacokinetic Population

The nicotine exposure analysis sets consist of all randomized subjects who give informed consent, completed at least one of the single uses of P4M3, and for whom at least one nicotine exposure parameter can be derived. Only subjects without major protocol deviations will be included in the nicotine exposure analysis sets.

Pharmacodynamic Population

The subjective measures analysis sets will include all subjects who used an IP and have pre-use (VAS for craving) and at least one post use (Adapted mCEQ, VAS for craving, or SQ) data.

Safety Population

The safety set population will consists of all the subjects who give informed consent and have at least one exposure to P4M3 (including the product test at Admission [Day -2]) and have at least one safety assessment post exposure.

6.2 Preliminary Data and Interim Analysis

An interim analysis using quality controlled preliminary PK data of plasma nicotine concentrations was performed. This analysis on the quality controlled data was conducted prior to database lock and the outcome of the analysis reviewed by the Sponsor.

During said interim analysis, the per protocol PK background-correction methodology was evaluated, as well as alternative PK modeling approaches. This was documented in a separate Clinical Pharmacology Statistical Analysis Plan prior to performing the final analysis. For full details, see the *Interim Pharmacokinetic Analysis Plan for Study P4M3-PK-02-US*, dated 12th September 2017, and the results from this evaluation in *Interim Pharmacokinetic Analysis Data Memo for Study P4M3-PK-02-US*, dated 15th September 2017.

7. INVESTIGATIONAL PRODUCT DESCRIPTIONS

7.1 Test Products:

The investigational products to be tested in this study are as follows:

Test Product	Short Description	Long Description
A	P4M3-1.7%	P4M3 with e-liquid concentrations of 1.7% nicotine without lactic acid
B	P4M3-1.7%LA	P4M3 with e-liquid concentrations of 1.7% nicotine with 1.1% lactic acid
C	P4M3-3%LA	P4M3 with e-liquid concentrations of 3% nicotine with 1.1% lactic acid
D	P4M3-4%LA	P4M3 with e-liquid concentrations of 4% nicotine with 2% lactic acid

The different variants of P4M3 will be provided by the Sponsor.

7.2 Reference Product:

Subject's own e-cigarette with e-liquid:

Commercially available, closed tank/cartridge e-cigarette.

Subjects will be asked to buy the anticipated amount of e-cigarette (e-liquid) for the study.

8. PHARMACOKINETIC ANALYSIS MATERIALS AND METHODS

The background-concentration correction and PK analysis will be performed by Certara.

8.1 Analysis Software

Nicotine exposure parameters will be derived from plasma nicotine *versus* time data by NCA using Phoenix® WinNonlin® version 7.0 or higher (Certara L.P. (Pharsight), St. Louis, MO).

8.2 Analysis Dataset

The final PK analysis is to be performed on the quality assured data, as provided by the bioanalytical laboratory, after database lock. The specifications of the PK analysis dataset will be described in a Data Transfer Agreement (DTA) that will be completed prior to the start of any PK analysis activities.

Any required data transformation for the PK analysis on the provided analysis PK set will be conducted by Certara using Phoenix® WinNonlin® version 7.0 or higher (Certara L.P. (Pharsight), St. Louis, MO).

8.3 Management of Missing Sampling or Concentration Data for NCA Analyses

8.3.1 Missing sampling or concentration data

Unless otherwise specified below, missing sampling or concentration values will not be imputed, but left missing in the calculation of derived PK parameters. As actual sampling times will not be available at the time of the interim analysis, nominal times rather than actual times will be used.

Any missing value for T-1 (prior to first product use) will be set to 0 for the PK calculations corresponding to an observation at the start of each product use (C_0) (Phoenix® WinNonlin® default setting for single dose data).

8.3.2 Concentration values below the lower limit of quantification

Values below the lowest limit of quantification (LLOQ) will be set to missing and ignored in the PK evaluation. The only exception to this rule will be the individual plasma concentration values between the start of product use and the first time point above LLOQ (i.e. during lag-time) are will be set to 0 and included in the PK evaluation.

8.3.3 PK Analysis Exclusions or Outliers

Exclusion of abnormal concentrations will be avoided, hence outlier values may only be excluded in the event there exists an explanation that clearly justifies such

exclusion (e.g. protocol violation, documented sample handling errors, stoppage of product use during fixed regimen, and/or analytical errors, best scientific judgment).

Any excluded data will be flagged in the individual data listings and if applicable, on figures. The reason for the exclusion will be documented. If the exclusion has a meaningful impact on the overall interpretation of the results, then it will also be discussed between Certara and PMI and fully documented.

8.4 Background-Concentration Correction Methodology

To minimize the potential bias in the plasma nicotine PK parameters for the *ad libitum* and fixed puffing regimens, background-concentration correction will be applied to the concentration data and derived PK parameters to adjust for carry-over effects. For nicotine exposure parameters, baseline (C_0) will be defined as the concentration immediately prior to T-1 for each session. The baseline correction will be implemented by calculating the nicotine exposure parameters using adjusted concentration values as described below:

The nicotine terminal elimination rate constant λ_z (and $t_{1/2z}$) will be estimated from the post-dose following the last product use PK samples (or early termination samples, if available) using a linear regression on the log concentrations from the terminal elimination phase.

The plasma nicotine background-corrected PK parameters will be derived by performing the NCA on the corrected concentrations.

For the purposes of background-correction of the plasma concentrations post-baseline the following formula will be applied: $cC_t = C_t - C_0 \cdot e^{-\lambda z \cdot t}$.

Where, C_t and cC_t are the observed and background-corrected plasma nicotine concentration at each time point, C_0 is the pre-use baseline concentration, λ_z is the Day 5 (or early termination, if available) terminal elimination rate constant and t is the actual time.

9. BIOMARKERS OF EXPOSURE TO NICOTINE

Serial blood samples (4 mL per sample) for determination of plasma nicotine will be taken as follows:

a) Fixed puffing (Morning: Day -1, Days 1 to 4):

A total of 10 blood samples will be taken for fixed puffing PK parameter estimation. One blood samples will be taken prior to the product use (T0) 15 minutes ± 5 minutes (T-1). Thereafter in relation to T0, blood will be drawn at the following time points: T1 after 2 minutes ± 30 seconds, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after

30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, and T9 after 4 hours ± 5 minutes.

b) *Ad libitum* use (Afternoon: Day -1, Days 1 to 4):

A total of 8 blood samples will be taken for the *ad libitum* PK parameter estimation. One blood sample will be taken prior to product use (T0) at 15 minutes ± 5 minutes (T-1). In relation to T0, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes and T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, and T7 after 4 hours ± 5 minutes.

c) Day 5 (or Early Termination Visit)

A total of 5 blood samples will be taken on Day 5. Blood samples will be taken in relation to T0 from *ad libitum* use on Day 4 at the following time points: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes, T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes and T5 after 24 hours ± 30 minutes.

10. SUBJECTIVE MEASURES AND HUMAN PUFFING TOPOGRAPHY

10.1 Subjective Measures

The Sensory Questionnaire (SQ; for both fixed puffing and *ad libitum* use) and Adapted mCEQ (for *ad libitum* use only) will be completed by each subject within 60 minutes after completion of product use on Day -1 to Day 4.

The VAS craving will be completed by each subject. The first assessment will be done prior to T0 of each fixed puffing regimen and *ad libitum* use on Days -1 to 4.

- Assessments will be performed at T0 for fixed puffing and at 4 minutes (± 2 minutes), 10 minutes (± 2 minutes), 15 minutes (± 2 minutes), 30 minutes (± 5 minutes), 1 hour (± 10 minutes), 2 hours (± 10 minutes), and 4 hours (± 10 minutes) on Day -1 to Day 4.

- Assessments will be performed at T0 for *ad libitum* use and at 10 minutes (± 2 minutes), 20 minutes (± 2 minutes), 30 minutes (± 5 minutes), 40 minutes (± 5 minutes), 1 hour (± 10 minutes), 2 hours (± 10 minutes), and 4 hours (± 10 minutes) on Day -1 to Day 4.

10.2 Human Puffing Topography

Fixed Puffing:

- Subjects will use their own e-cigarette (Day -1) and P4M3 (Mornings of Days 1 to 4) with the HPT device physically connected during the fixed puffing regimen of 12 puffs with 30 seconds (± 5 seconds) between each puff over

approximately 6 minutes. The used e-liquid cartridges will be collected for assessment of e-liquid use.

Ad libitum Use:

- Subjects will use their own e-cigarette (Day -1) and P4M3 (afternoons of Days 1 to 4) with HPT device physically connected during the *ad libitum* regimen for 60 minutes. The used e-liquid cartridges will be collected for assessment of e-liquid use.

11. ANALYTICAL DATA SUMMARIZATION AND STATISTICAL ANALYSIS

11.1 Analytical Methodology

Biomarkers of Exposure to Nicotine

Blood samples (4 mL) for determination of nicotine concentrations will be drawn from subjects following a 5-minute rest.

Nicotine PK parameters will be derived from both the observed plasma nicotine versus time concentration data, as well as the background-corrected plasma nicotine concentrations (as described in Section 8.4) using noncompartmental analysis principles. The corresponding total exposure parameters or AUCs (including $cAUC_{(0-4h)}$, $AUCb_{(0-4h)}$, etc.) will be calculated following the conventional linear trapezoidal method. All parameters will be estimated using the predefined Phoenix® WinNonlin® calculation and interpolation formulas, therefore "user defined" formulas will not be used.

The actual blood sampling times post-exposure collected in the case report form (CRF) will be used in the computation of the PK parameters where available, with the exception of pre-exposure sampling time which will be considered as time zero (T_0) for both *ad libitum* and fixed puffing regimens. If an actual sampling time is missing from the dataset, the corresponding nominal sampling time will be used instead.

In addition, the following rules for reporting of λ_z and terminal elimination half-life ($t_{1/2z}$) will be applied:

1. The regression analysis should contain data from at least 3 different time points in the terminal phase and as many data points as possible (always including the last quantifiable concentration but excluding the concentration at t_{max}), consistent with the assessment of a straight line on the log-transformed scale.

2. The coefficient of determination Adjusted-R^2 should be larger than or equal to 0.700.

Subjective Measures and Scoring

The SQ, Adapted mCEQ, VAS craving, and need to cough questionnaires will be completed using paper CRF.

Human Puffing Topography

On Day -2, subjects will be debriefed on the P4M3 product and will perform a product test with P4M3-1.7% for a maximum of 10 minutes. P4M3 will be physically connected to the puffing topography device without recording of parameters (HPT device switched off) and test the product for a maximum of 10 minutes. On Days -1 through 4, subjects will use the e-cigarette coupled to a portable measurement device to gather smoking topography profiles (*i.e.,* number of puffs per cigarette, puff volume, puff duration, puff peak flow, and inter-puff interval).

After training on Admission Day (Day -2), at Baseline (Day -1), subjects will be instructed to use their own closed tank/cartridge e-cigarette using a fixed puffing regimen in the morning and subsequently, to use it *ad libitum* for 60 minutes in the afternoon. The start time of the product use for each fixed puffing regimen and *ad libitum* use will be defined as start of the first puff (T0). T0 will be at approximately the same time in the morning (± 30 minutes) for fixed puffing regimen and at approximately the same time in the afternoon (± 30 minutes) for *ad libitum* use on Days 1 to 4.

11.2 Data Summarization and Presentation

Biomarkers of Exposure to Nicotine

Total and background-corrected plasma nicotine concentration versus time profiles will be presented graphically and summarized in tables.

The plasma nicotine PK parameters will be determined from the concentration-time profiles for all evaluable subjects according to standard Non-Compartmental Analysis (NCA) methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. All analyses and summaries will be performed separately for fixed puffing and *ad libitum* use.

Unless otherwise specified, PK parameters will be evaluated between T0 to 4 hours after product use. This is to ensure consistency when comparing PK parameters accross treatment periods.

The following baseline-corrected PK parameters will be calculated, as per protocol PK endpoints, for the *ad libitum* (Table 1) and fixed (Table 2) regimens:

Table 1 Background-corrected *Ad Libitum* Plasma Nicotine PK Parameters

Symbol/Term	Unit	Definition
cC_{peak}	ng/mL	Background-corrected peak plasma nicotine concentration.
t_{peak}	min	Time to peak plasma nicotine concentration.
cC_{trough}	ng/mL	Background-corrected trough plasma nicotine concentration.
$cC_{average}$ [a]	ng/mL	Background-corrected average of plasma nicotine concentration between T0 to 1 hour.
$cAUC_{(0-4h)}$	ng·h/mL	Background-corrected area under the concentration-time curve from the start of product use to 4 hours.

a $cC_{average}$ is calculated by estimating the $cAUC_{(0-1h)}$ [background-corrected area under the concentration-time curve from the start of product use to 1 hour] divided by 1 hour. As a result, $cC_{average}$ is the same as $cAUC_{(0-1h)}$.

Table 2 Background-corrected Fixed Regimen Plasma Nicotine PK Parameters

Symbol/Term	Unit	Definition
cC_{max}	ng/mL	Background-corrected maximum plasma nicotine concentration from T0 to 4 hours.
t_{max}	min	Time to the maximum concentration between T0 to 4 hours.
$cAUC_{(0-4h)}$	ng·h/mL	Background-corrected area under the concentration-time curve from T0 to 4 hours.

The following λ_z-related plasma nicotine PK parameters, including $t_{1/2z}$, will also be calculated using plasma nicotine concentrations up to 24 hours following the last product use will also be calculated and reported, as shown in Table 3:

Table 3 Nicotine λ_z-related Parameters Following Last P4M3 Product Use (Days 4 to 5)

Symbol/Term	Unit	Definition
Adjusted-R^2	n/a	Adjusted coefficient of determination for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z.
No. points λ_z	n/a	Number of points used in computing λ_z. If λ_z cannot be estimated, zero.
λ_z upper	hr	Upper limit on Time for values to be included in the calculation of λ_z.
λ_z lower	hr	Lower limit on Time for values to be included in the calculation of λ_z.
λ_z	hr^{-1}	Terminal elimination rate constant.
$t_{1/2z}$	hr	Terminal elimination half-life.

The following additional unadjusted plasma nicotine PK parameters will also be calculated and reported, as shown in Table 4, for *ad libitum*, Table 5, for fixed regimens, as follows:

Table 4 *Ad Libitum* Plasma Nicotine PK Parameters

Symbol/Term	Unit	Definition
C_{peak}	ng/mL	Peak plasma nicotine concentration.
t_{peak}	min	Time to peak plasma nicotine concentration.
C_{trough}	ng/mL	Trough plasma nicotine concentration (after T0).
$C_{average}$ [a]	ng/mL	Average of plasma nicotine concentrations between T0 to 1 hour.
$AUC_{(0-4h)}$	ng·h/mL	Area under the concentration-time curve from T0 to 4 hours.
$AUCb_{(0-4h)}$	ng·h/mL	Area under the concentration-time curve that is above the corrected baseline from T0 to 4 hours.

a $C_{average}$ is calculated by estimating the $cAUC_{(0-1h)}$ [background-corrected area under the concentration-time curve from the start of product use to 1 hours] divided by 1 hour. As a result, $C_{average}$ is the same as $AUC_{(0-1h)}$.

Table 5 Fixed Regimen Plasma Nicotine PK Parameters

Symbol/Term	Unit	Definition
C_{max}	ng/mL	Maximum plasma nicotine concentration
t_{max}	ng/mL	Time to the maximum concentration (after T0)
$AUC_{(0-4h)}$	ng·h/mL	Area under the concentration-time curve from T0 to 4 hours

Subjective Measures Analysis

Sensory Questionnaire

The Sensory Questionnaire (Rose *et al*, 2010) will be completed by each subject. The SQ will be used to assess product's strength (on the tongue, in the nose, in the back of the mouth and throat, in windpipe, in chest), harshness, similarity with own brand of e-cigarette and liking. This questionnaire is well established and has been used in numerous studies for evaluation of smoking experiences. Subjects will be asked to assess the 8 items of the questionnaire on a 7-point scale, ranging from "not at all" to "extremely". No total score will be calculated. The assessments will be done within 60 minutes after completion of product use for each fixed puffing regimen and *ad libitum* product use for subjects' own e-cigarette and P4M3 variants.

The SQ assesses the subject's opinion on the following sensory parameters:

- Puff information i.e., how they liked the puffs, harshness of puffs, and similarity to own brand;
- Strength of puffs on tongue, nose, back of mouth and throat, windpipe, and chest.

Each question will be considered as a 7-point scale, where 1 = not at all and 7 = extremely, and treated as a continuous variable.

Adapted mCEQ

The adapted mCEQ (Rose *et al*, 1998) will be completed by each subject. The adapted mCEQ adapts the wording of mCEQ items to RRPs, following a similar approach of Hatsukami (Hatsukami *et al*, 2013) with the Product Evaluation Scale (PES) which is an adaptation of the mCEQ for oral tobacco products.

Items are assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity on that scale. The assessments will be done within 60 minutes after completion of product use for each fixed puffing regimen and ad libitum product use for subjects' own e-cigarette and P4M3 variants.

The Adapted mCEQ will be considered as a 7-point scale, where 1 = not at all and 7 = extremely, and treated as a continuous variable. The responses to the adapted mCEQ questions will be presented as the following subscale scores based on Cappelleri (Cappelleri *et al*, 2007):

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

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

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

d) Enjoyment of the sensory sensation: response score from question 3;

e) Craving reduction: response score from question 11.

The subscales scores will be derived by averaging the relevant individual non-missing item scores if at least 50% are non-missing, otherwise the subscale score will be set to missing.

VAS craving

Responses to the Craving questionnaire will be recorded as VAS scores and summarized by study product and time point. The original VAS score will be treated as continuous variables

The parameters for the Craving questionnaires will be presented as follow:

$E_{max(0\text{-}4h)}$ For response to Craving questions, the maximum reduction in VAS score between pre-use and post-use (i.e., $VAS_{pre\text{-}use} - VAS_{post\text{-}use}$) for each product use.

$AUC_{(0\text{-}4h)}$ Area under the VAS craving score-time curve from the start of fixed puffing product use to 4 hours.

Human Puffing Topography

The following HPT parameters will be recorded:

- Per-Puff Parameters:

Description	Variable	Unit
Puff number	Ni	
Puff volume	Vi	mL
Puff duration	Di	s
Average flow [Vi/Di]	Qmi	mL/s
Peak flow	Qci	mL/s
Inter puff interval	Ii	s
Sum of Ii and Di	DFi	s
Work [INT Pmi*FinalFlow*dt]	Wi	mJ
Average pressure drop	Pmi	mmWG
Peak pressure drop	Pci	mmWG
Average resistance [Pmi/Qmi]	Rmi	mmWG/mL/s
Peak resistance [Pci/Qci]	Rci	mmWG/mL/s
Number of peaks	Pn	

- Per-product use parameters:

Description	Variable	Formula	Unit
Total number of puffs	NPC	∑ Ni	
Total puff volume	TVOL	∑ Vi	mL
Average puff volume	AvgVi	∑ Vi / NPC, i=1 ... NPC	mL
Average puff duration	AvgDi	∑ Di / NPC, i=1 ... NPC	s
Total puff duration	TDi	∑ Di	s
Average flow	AvgQmi	∑ Qmi / NPC, i=1 … NPC	mL/s
Average Peak flow	AvgQci	∑ Qci / NPC, i=1 … NPC	mL/s
Total inter puff interval	TIi	∑ Ii	s
Average inter puff interval	AvgIi	∑ Qci / NPC, i=1 … NPC	s
Total product use duration	TDFi	∑ DFi	s
Total Work	TWi	∑Wi	mJ
Average Work	AvgWi	∑Wi / NPC, i=1 … NPC	mJ
Average pressure drop	AvgPmi	∑Pmi / NPC, i=1 … NPC	mmWg
Average Peak pressure drop	AvgPci	∑Pci / NPC, i=1 … NPC	mmWg
Product Use Intensity	SMINT	TVOL/TDFi	mL/s
Puffing Time Index	PTI	(100*TDi)/TDFi	%
Puff Frequency	PFeq	NPC/(TDFi/60)	

11.3 Statistical Methodology

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

Descriptive Statistics
SAS software (version 9.3 or higher, Cary, North Carolina) will be used for all data presentation and summarization including statistical analyses, summary tables, graphs, and data listings. Celerion will generate all tables, figures, listings, and statistical analyses.

Plasma nicotine concentrations and PK parameters will be summarized by study product and listed by subject. The following descriptive statistics will be included: number of subjects (n), number and percent of subjects with missing data, arithmetic means and standard deviations (mean and SD), median, minimum and maximum. For log normally distributed PK parameters, geometric mean, geometric CV% will also

be presented (note: categorical variables will be summarized by frequency statistics [number and percentage]). For PK parameters relating to sampling times (e.g. t_{max}), and count data, only median and range (minimum and maximum) will be presented.

Adapted mCEQ subscale scores, SQ answers, and VAS craving assessment will be summarized by product and product use [fixed puffing (SQ and VAS) and after *ad libitum* use (mCEQ, SQ, and VAS)] with descriptive statistics and displayed graphically. HPT parameters will be summarized by product use [fixed puffing or *ad libitum* use] with geometric mean, % coefficient of variation (%CV), and 90% confidence intervals (CIs). The following descriptive statistics will be included for all endpoints: sample size (n), number and percent of subjects with missing data, arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum. For log normally distributed endpoints, geometric mean, geometric CV% will also be presented (note: categorical variables will be summarized by frequency statistics [number and percentage]). All analyses and summaries will be performed separately for fixed puffing and *ad libitum* use.

The level of precision for the summary statistics will be as follows:

- n without a decimal;
- minimum/maximum in same precision as in the database;
- mean/median/geometric mean with one more decimal than minimum/maximum;
- SD with one more decimal than mean/median;
- %CV/geometric CV% with one decimal;
- 90% CI with two decimals.

Where individual data points are missing because of discontinuations, withdrawals or other reasons, the data will be summarized based on reduced denominators. Missing data will be treated as missing at random and no data imputation will be conducted.

Analysis of Variance

For the 60-minute *ad libitum* uses, an ANOVA will be conducted on logarithmically transformed cC_{peak}, $cC_{average}$, and $cAUC_{(0\text{-}4h)}$ to statistically evaluate the exposure differences between products at an alpha-level of significance of 0.05. The model will be adjusted for sex with product use as a fixed effect and subjects as a random effect. Wilcoxon signed-rank test will be used to compare t_{peak} between the test (P4M3 variant) and reference (subject's own e-cigarette) products.

The following SAS codes will be used for the ANOVA analysis.

```
Proc Mixed data=< >;
Class product sex,
Model ln_parameter = product sex/ddfm=kr;
```

```
Random Subject;
LSmeans product/CL pdiff alpha=0.05;
Estimate "P4M3-1.7% versus Subject Own e-cigarette" product 1 0 0 0 -1/CL
alpha=0.10;
Estimate "P4M3-1.7%LA versus Subject Own e-cigarette" product 0 1 0 0 -1/CL
alpha=0.10;
Estimate "P4M3-3%LA versus Subject Own e-cigarette" product 0 0 1 0 -1/CL
alpha=0.10;
Estimate "P4M3-4%LA versus Subject Own e-cigarette" product 0 0 0 1 -1/CL
alpha=0.10;
Run;
```

The following SAS codes will be used for Wilcoxon signed-rank test:

```
Proc univariate data = < >;
 Var diff;
Run;
```

Note: the variable diff is the difference between the P4M3 product and subject's own cigarette. As there are four P4M3 variant, the analysis will be run four times (one for each product.

For the fixed puffing regimens, the ratio of geometric mean nicotine exposure normalized $cAUC_{(0\text{-}4h)}$ and cC_{max} for each P4M3 variant in reference the subject's own e-cigarette will be presented with associated 90% CIs. The theoretical nicotine exposure will be used for the purposes of parameter normalization. In order to evaluate the PK parameters of the P4M3 variants with subjects' own e-cigarette, an ANOVA will be conducted on logarithmically transformed $cAUC_{(0\text{-}4h)}$ and cC_{max}. The model will include sex and product use as fixed effects and subjects as a random effect. For each P4M3 variant, the geometric LSM P4M3 variant:e-cigarette ratios will be presented with 90% CIs.

Theoretical nicotine exposure will be calculated as follows: Total puff volume [mL] (from the per-product HPT data) x nicotine [µg/mL]. The amount of nicotine in the P4M3 variants will be as follow:

P4M3-1.7%	61.9 µg/puff
P4M3-1.7%LA	69.6 µg/puff
P4M3-3%LA	122.3 µg/puff
P4M3-4%LA	159.4 µg/puff

The standard puff volume will be 55 mL.

In addition, for the fixed regimens, the impact of the lactic acid will be evaluated for the PK parameters, using an ANOVA on logarithmically transformed $cAUC_{(0\text{-}4h)}$ and

cC_{max}, adjusting for sex, with sequence, period, and product as fixed effects and subject nested within sequence as a random effect. The geometric LSM P4M3-1.7%LA:P4M3-1.7% ratios will be presented with 90% CIs. Wilcoxon signed-rank test will be used to compare t_{max} between the study products.

The following SAS codes will be used for the analysis.

```
Proc Mixed data=< >;
Class sequence period product sex,
Model ln_parameter = sequence period product sex/ddfm=kr;
Random Subject(sequence);
LSmeans product/CL pdiff alpha=0.05;
Estimate "P4M3-1.7%LA versus P4M3-1.7%" product -1 1/CL alpha=0.05;
Run;
```

The Adapted mCEQ subscale scores and SQ answers (separately for fixed puffing and *ad libitum* use) will be analyzed using an ANOVA adjusted for sex, with product use as a fixed effect and subject as a random effect. Least-square means (LSMs) and 90% confidence intervals will be provided for the study products. LSM difference, 90% confidence intervals for LSM difference and p-values will be provided for the study product comparisons. The comparisons of interest will include each P4M3 product compared to the subject own e-cigarette. No adjustment will be made for multiple comparisons.

The following SAS codes will be used for the analysis.

```
Proc MIXED data=< >;
Class Subject Product Sex;
Model Score = Product Sex/ddfm=KR;
Random Subject;
LSMeans Product/diff CL Alpha=0.10;
Estimate "P4M3-1.7% vs Subject Own e-cigarette" Product 1 0 0 0 -1/CL alpha=0.1;
Estimate "P4M3-1.7%LA vs Subject Own e-cigarette" Product 0 1 0 0 -1/CL
alpha=0.1;
Estimate "P4M3-3%LA vs Subject Own e-cigarette" Product 0 0 1 0 -1/CL
alpha=0.1;
Estimate "P4M3-4% LA vs Subject Own e-cigarette" Product 0 0 0 1 -1/CL
alpha=0.1;
Estimate "P4M3-1.7% LA vs P4M3-1.7%" Product -1 1 0 0 0/CL alpha=0.1;
Run;
```

The VAS craving scores will be assessed using an Analysis of Covariance (ANCOVA) model with product use, sex, baseline value prior to product use, the interaction of product and time point as fixed effects, and subject as a random effect, and the assessment time points as repeated measurements. The interaction term will

be removed if p > 0.1. The summary statistics will include least square means as well as arithmetic means. Additionally, the AUC for the VAS craving score will be analyzed using the same approach as for the PK parameters. The model will be adjusted for sex and baseline value prior to product use with product use as a fixed effect and subject as a random effect. No adjustment will be made for multiple comparisons.

The following SAS codes will be used for the analysis of the scores.

```
Proc MIXED data=< >;
Class Subject Product Time Sex;
Model Score = Product Time Product*Time Sex Baseline/ddfm=KR;
Repeated Time/type=UN Subject=Subject(Product);
Random Subject;
LSMeans Product|Time/diff CL Alpha=0.10;
Run;
```

The following SAS codes will be used for the analysis of AUC.

```
Proc MIXED data=< >;
Class Subject Product Sex;
Model Score = Product Sex Baseline/ddfm=KR;
Random Subject;
LSMeans Product/diff CL Alpha=0.10;
Estimate "P4M3-1.7% vs Subject Own e-cigarette" Product 1 0 0 0 -1/CL alpha=0.1;
Estimate "P4M3-1.7%LA vs Subject Own e-cigarette" Product 0 1 0 0 -1/CL
alpha=0.1;
Estimate "P4M3-3%LA vs Subject Own e-cigarette" Product 0 0 1 0 -1/CL
alpha=0.1;
Estimate "P4M3-4% LA vs Subject Own e-cigarette" Product 0 0 0 1 -1/CL
alpha=0.1;
Run;
```

Graphical Exploratory Analysis

The dose-proportionality / effect of lactic acid of the P4M3 variants versus nicotine exposure PK parameters will be investigated graphically on an exploratory basis for the *ad libitum* and fixed puffing regimens separately.

The following plots will be generated:

- Boxplot of cC_{peak} *versus* P4M3 variant [*ad libitum*]
- Boxplot of cC_{max} *versus* P4M3 variant [fixed]
- Boxplot of cC_{trough} *versus* P4M3 variant [*ad libitum*]
- Boxplot of $cAUC_{(0\text{-}4h)}$ *versus* P4M3 variant [fixed and *ad libitum*]

To evaluate the association between theoretical nicotine exposure and PK parameters (background-corrected and unadjusted) of the P4M3 variants from the 60 minutes *ad libitum* use and the fixed puffing regimen, the following graphical analysis will be performed:

- Scatterplot of cC_{peak} *versus* R_0 with LOESS smoothing line, where R_0 is defined as the theoretical rate of nicotine inhalation calculated for each product use [R_0 = theoretical nicotine exposure/total puffing duration] (60 minutes *ad libitum* use only)
- Scatterplot of cC_{max} *versus* R_0 (as defined above) with LOESS smoothing line (fixed puffing regimen only)
- Scatterplot $cAUC_{(0\text{-}4h)}$ *versus* theoretical nicotine exposure with LOESS smoothing line (60 minutes *ad libitum* use and fixed puffing regimen)

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 summarized using n, arithmetic 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.

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

No inferential statistics will be performed.

12.1 Subject Discontinuation

Subjects will be summarized by the number of subjects who enrolled, completed, and discontinued the study (with discontinuation reasons) by randomized product sequence and overall.

12.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) by randomized product sequence and overall. Age will be derived from date of birth to the informed consent date.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) for each randomized product sequence and overall.

12.3 Smoking History

Descriptive statistics will be calculated for continuous variables (number of years smoked) by randomized product sequence and overall.

Frequency counts will be provided for categorical variables for each randomized product sequence and overall.

12.4 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 20.0. AEs will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, product, severity, relationship to study product, and action; however, only product use-emergent AEs (PUEAEs) will be summarized. Adverse events after admission and prior to Day -1 and occurred on Day -1 will be summarized separately under admission (P4M3-1.7%) and subject's own e-cigarette, respectively.

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

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

All AEs will be summarized by product (fixed puffing and ad libitum use combined) and overall. The number and percentage of subjects with AEs, SAEs, and device events will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to discontinuation, AEs leading to death, AEs by relatedness to product exposure (with and without laboratory related AEs), AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events. Due to the laboratory schedule in this study, Day -2 labs AEs not be linked with P4M3 because are before

any administration of the product. Day 2 will be linked to P4M3-1.7% and Day 5 with P4M3-4%.

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

12.5 Clinical Laboratory Tests (Clinical chemistry, Hematology, Urinalysis)

Clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) will be performed at Screening, Admission (Day -2), Day 2, and at the time of discharge (Day 5) or as early termination assessments, as applicable.

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

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by assessment time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected on Admission (Day -2). 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 (systolic and diastolic blood pressure, pulse rate, and respiratory rate) will be measured at the Screening Visit, on Admission (Day -2), and on every day of confinement (Days -1 through 5, pre product use and 60 minutes [±10 minutes] post end of product use and at Discharge), or at early termination. All parameters will be measured in the supine position after the subject has rested for at least 5 minutes.

Descriptive statistics will be reported for vital sign measurements (blood pressure, pulse, respiration, and temperature) by time point for Screening, Admission, and at the time of discharge. For Days -1 through 4, descriptive statistics will be reported for vital sign measurements by product at pre product use, 60 minutes post product use as well as change from pre product use. Post product use recheck values will not be used for calculation of descriptive statistics. 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

An ECG will be recorded at Screening and at Discharge (Day 5) or at early termination. The ECG testing will be performed as per the investigational site standard practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

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

Descriptive statistics will be presented for each ECG parameter by assessment time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected at Screening. Post product use unscheduled events or rechecks will not be included in summaries. Similarly early termination results will not be included in summaries. A shift table will be developed to compare the frequency of the results at baseline (normal, abnormal – clinically not relevant, or abnormal – clinically relevant) with the respective post product use results.

12.8 Concomitant Medications and Procedures

All medications will be listed by subject and sequence using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization Drug Dictionary) Version 01MAR2017. Concomitant procedures recorded during the study will be listed by subject. Concomitant Medications will be summarized using frequency count by product sequence.

12.9 Physical Examination

A physical examination will be conducted at the Screening Visit, at Admission (Day -2) and at the Day of Discharge (Day 5) or at early termination. All data found in the CRF will be listed.

12.10 Spirometry

Spirometry with and without a short-acting bronchodilator will be done at the Screening Visit to evaluate inclusion/exclusion criteria. Spirometry without a bronchodilator will be performed at the time of discharge on Day 5 or at early termination.

For spirometry, assessed parameters will include FEV_1, FEV_1 % Predicted, FVC, and FEV_1/FVC. Descriptive statistics will be presented for each spirometry parameter by assessment time point and measurement method.

12.11 Cough Assessment Questionnaire

Subjects will be asked if they have experienced a need to cough within 30 minutes after the P4M3-1.7% product test at Admission (Day -2), within 30 minutes after each fixed puffing regimen and *ad libitum* use on Days -1 to 4, and at discharge or at early termination. If the answer is 'yes', they will be asked to complete a cough assessment questionnaire (which includes a VAS, three Likert scales, and an open question).

The VAS will assess how bothersome cough is to the subject ranging from 'not bothering me at all' to 'extremely bothersome'.

Furthermore, subjects will be asked to assess the intensity and frequency of cough and the amount of sputum production on Likert scales:

- The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5:
  1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe.
- The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5:
  1 = rarely; 2 = sometimes; 3 = fairly often; 4 = often; 5 = almost always.
- The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3:
  0 = no sputum; 1 = a moderate amount of sputum; 2 = a larger amount of sputum; 3 = a very large amount of sputum

Frequency count tables will be generated for the responses to the cough assessment questionnaire by time point and product.

13. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The $cAUCb_{(0\text{-}4h)}$ term is the per protocol parameter nomenclature. As baseline nicotine concentrations (C_0) will be background-corrected, and thus equal to zero, $cAUCb_{(0\text{-}4h)}$ will be analogous to $cAUC_{(0\text{-}4h)}$. The term $cAUC_{(0\text{-}4h)}$ will thus be used to avoid redundant terminology, but a footnote will be added in summary tables and listings identifying it as the per protocol $cAUCb_{(0\text{-}4h)}$ parameter.

The term C_{trough} was originally intended for baseline adjustments of plasma nicotine concentrations as it was originally defined as the concentration at T0. It was later redefined as the lowest concentration after T0. Thus, C_{trough} cannot be used for baseline adjustments anymore. The term C_{trough} was removed from the ANOVA for PK parameters where C_{trough} was a fixed effect and from the '$cC_{peak} - cC_{trough}$' term.

In the protocol, the term $cC_{average}$ was included by error in the ANOVA of PK parameters in the fixed regimen. $cC_{average}$ was never intended to be calculated for the fixed regimen; thus, $cC_{average}$ was removed from the ANOVA.

Exploratory analyses for dose-proportionality of the e-liquid concentrations (with lactic acid only) versus nicotine exposure PK parameters will be conducted although the protocol indicated no exploratory analyses were planned.

For $cAUC_{(0-4h)}$ and cC_{max} comparison between P4M3-1.7%LA and P4M3-1.7%, the protocol mentioned the subject nested within sequence will be a fixed effect in the model. It was updated to a random effect in the statistical model.

Protocol indicated that "only P4M3 variants emergent AEs will be summarized by product variant (fixed puffing regimen and ad libitum use will be combined at the product variant level) and P4M3 overall". In the SAP, the AEs emergent to all products will be summarized which also includes subject's own brand e-cigarette.

Protocol indicated that "due to the laboratory schedule in this study, any lab related AEs will be assigned to P4M3 4% nicotine concentration". It was updated in the SAP as "due to the laboratory schedule in this study, Day -2 labs AEs not be linked with P4M3 because are before any administration of the product. Day 2 will be linked to P4M3-1.7% and Day 5 with P4M3-4%.".

In the protocol, it indicated that Descriptive statistics will be summarized for change from baseline vital signs. In the SAP, the change from baseline to discharge was not presented. For Days -1 through 4, descriptive statistics will be reported for vital sign measurements by product at pre product use, 60 minutes post product use as well as change from pre product use.

The other analyses described in this SAP are aligned with those analyses described in the protocol.

14. REFERENCES

Rose *et al,* 2010

Rose JE, Turner JE, Murugesan T, Behm FM, Laugesen M. Pulmonary delivery of nicotine pyruvate: sensory and pharmacokinetic characteristics. Experimental and clinical psychopharmacology. 2010;18(5):385-94.

Rose *et al,* 1998

Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. Experimental and clinical psychopharmacology. 1998;6(3):331-43

Cappelleri *et al*, 2007

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

15. 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 Subjective measures, HPT, and Safety summary tables and figures will be generated using SAS® Version 9.3 or higher, as appropriate.

15.1 In-text Summary Tables and Figures

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

Section 10:

Table 1 Subject Disposition Summary (Safety Population)

Table 2 Demographic Summary (Safety Population)

Section 11:

Pharmacokinetic

Table 3 Summary of Background-Corrected Plasma Nicotine PK Parameters Following *Ad Libitum* Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers

Table 4 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameters (cC_{peak}, $cC_{average}$ and $cAUC_{(0\text{-}4h)}$) Following *Ad Libitum* Use of P4M3 Variants Versus Subject Own e-Cigarette

Table 5 Wilcoxon Signed-Rank Test for Background-Corrected t_{peak} Following *Ad Libitum* Use of P4M3 Variants Versus Subject Own e-Cigarette

Table 6 Summary of Background-Corrected Plasma Nicotine PK Parameters Following Fixed Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers

Table 7 Geometric Mean Ratios (90% CIs) of the Nicotine Exposure-Normalized Plasma PK Parameters cC_{max} and $cAUC_{(0\text{-}4h)}$ Following Fixed Regimen Use for P4M3 Variants *versus* Subject's Own e-Cigarette

Table 8 Wilcoxon Signed-Rank Test for Background-Corrected t_{max} Following Fixed Regimen Use of P4M3 Variants Versus Subject Own e-Cigarette

Figure 10 Boxplot of $cAUC_{(0\text{-}4h)}$ *versus* P4M3 Variants Following Fixed Regimen Use

Note:

- Figures 6 through 10 are boxplots of PK parameters versus the 5 products.
- The x-axis will be 'Subject Own e-Cigarette", "P4M3-1.7%", "P4M3-1.7%LA", "P4M3-3.3%LA", and "P4M3-4%LA". The y-axis will be plasma PK parameters (units).
- Source tables:
  - Figure 6 through 8: Listing 15.3.6.2.7
  - Figure 9 through 10: Listing 15.3.6.2.8
- No figure shells are provided but will be generated during the tables/figures production.

Figure 11 Scatterplot of cC_{peak} *versus* Theoretical Rate of Nicotine Inhalation (R_0) Following *Ad Libitum* Regimen Use with LOESS Smoothing Line and Line of Unity

Figure 12 Scatterplot $cAUC_{(0\text{-}4h)}$ *versus* Theoretical Nicotine Exposure Following *Ad Libitum* Regimen Use with LOESS Smoothing Line and Line of Unity

Figure 13 Scatterplot of cC_{max} *versus* Theoretical Rate of Nicotine Inhalation (R_0) Following Fixed Regimen Use with LOESS Smoothing Line and Line of Unity

Figure 14 Scatterplot $cAUC_{(0\text{-}4h)}$ *versus* Theoretical Nicotine Exposure Following Fixed Regimen Use with LOESS Smoothing Line and Line of Unity

Note:

- Figures 11 through 14 are scatterplots of PK parameters versus theoretical parameters.
- The x-axis will be "Theoretical Rate of Nicotine Inhalation (R_0)" and "Theoretical Nicotine Exposure". The y-axis will be plasma PK parameters (units).
- Source tables:
  - Figure 11 and 12: Listing 15.3.6.2.7 and 15.3.6.2.10

  - Figure 13 and 14: Listing 15.3.6.2.8 and 15.3.6.2.11

- No figure shells are provided but will be generated during the tables/figures production.

Pharmacodynamic and Human Puffing Topography

Table 11	Summary of the Responses to the Sensory Questionnaire (Pharmacodynamic Population)
Table 12	Statistical Comparisons of the Responses to the Sensory Questionnaire (Pharmacodynamic Population)
Table 13	Summary of the Responses to the Adapted modified Cigarette Evaluation Questionnaire (Pharmacodynamic Population)
Table 14	Statistical Comparisons of the Responses to the Adapted modified Cigarette Evaluation Questionnaire (Pharmacodynamic Population)
Table 15	Summary of the VAS Craving Assessment (Pharmacodynamic Population)
Table 16	Statistical Comparisons of the VAS Craving Assessment (Pharmacodynamic Population)
Table 17	Summary of Human Puffing Topography Per-Puff Parameters (Pharmacodynamic Population)
Table 18	Summary of Human Puffing Topography Per-Product Use Parameters (Pharmacodynamic Population)
Figure 15	VAS Craving Assessment versus Time by Product (Fixed Puffing) (Pharmacodynamic Population)
Figure 16	VAS Craving Assessment versus Time by Product (*Ad Libitum* Use) (Pharmacodynamic Population)

Section 12:

Table 19	Adverse Event Frequency by Product - Number of Subjects Reporting the Event (% of Subjects Who Used Study Product) (Safety Population)

15.2 Section 15 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 15 of the report as a separate appendix. Table and figure titles may be renumbered as appropriate during the compilation of the report.

15.1 Figures

15.1.1 Primary Endpoints

Figure 15.1.1.1 Plasma Nicotine Mean (SD) Concentration-Time Profiles following *Ad Libitum* Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [Top Panel: Linear-Linear, Top Panel: Semi-Log]

Figure 15.1.1.2 Early Plasma Nicotine Mean (SD) Concentration-Time Profiles following *Ad Libitum* Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [truncated at 1 hour post-use]

Figure 15.1.1.3 Plasma Nicotine Mean (SD) Concentration-Time Profiles following Fixed Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [Panel A: Linear-Linear, Panel B: Semi-Log]

Figure 15.1.1.4 Early Plasma Nicotine Mean (SD) Concentration-Time Profiles following Fixed Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [truncated at 1 hour post-use]

Figure 15.1.1.5 Semi-Log Plasma Nicotine Mean (SD) Concentration-Time Profile after the Last Ad Libitum P4M3-4%LA Use on Day 4

15.1.2 Secondary Endpoints

15.1.2.1 Biomarkers of Exposure to Nicotine

Figure 15.1.2.1.1 Boxplot of C_{peak} *versus* P4M3 Variants Following *Ad Libitum* Regimen Use

Figure 15.1.2.1.2 Boxplot of C_{trough} *versus* P4M3 Variants Following *Ad Libitum* Regimen Use

Figure 15.1.2.1.3 Boxplot of $AUCb_{(0\text{-}4h)}$ *versus* P4M3 Variants Following *Ad Libitum* Regimen Use

Figure 15.1.2.1.4 Boxplot of C_{max} *versus* P4M3 Variants Following Fixed Regimen Use

Figure 15.1.2.1.5 Boxplot of $AUC_{(0\text{-}4h)}$ *versus* P4M3 Variants Following Fixed Regimen Use

Note:

- Figures 15.1.2.1.1 through 15.1.2.1.5 are boxplots of PK parameters versus the 5 products.
- The x-axis will be 'Subject Own e-Cigarette", "P4M3-1.7%", "P4M3-1.7%LA", "P4M3-3.3%LA", and "P4M3-4%LA". The y-axis will be plasma PK parameters (units).
- Source tables:
  - Figure 15.1.2.1.1 through 15.1.2.1.3: Listing 15.3.6.2.5
  - Figure 15.1.2.1.4 through 15.1.2.1.5: Listing 15.3.6.2.6
- No figure shells are provided but will be generated during the tables/figures production.

Figure 15.1.2.1.6 Scatterplot of C_{peak} *versus* Theoretical Rate of Nicotine Inhalation (R_0) Following *Ad Libitum* Regimen Use with LOESS Smoothing Line and Line of Unity

Figure 15.1.2.1.7 Scatterplot $AUCb_{(0\text{-}4h)}$ *versus* Theoretical Nicotine Exposure Following *Ad Libitum* Regimen Use with LOESS Smoothing Line and Line of Unity

Figure 15.1.2.1.8 Scatterplot of C_{max} *versus* Theoretical Rate of Nicotine Inhalation (R_0) Following Fixed Regimen Use with LOESS Smoothing Line and Line of Unity

Figure 15.1.2.1.9 Scatterplot $AUC_{(0\text{-}4h)}$ *versus* Theoretical Nicotine Exposure Following Fixed Regimen Use with LOESS Smoothing Line and Line of Unity

Note:

- Figures 15.1.2.1.6 through 15.1.2.1.9 are scatterplots of PK parameters versus theoretical parameters.
- The x-axis will be "Theoretical Rate of Nicotine Inhalation (R_0)" and "Theoretical Nicotine Exposure". The y-axis will be plasma PK parameters (units).

- Source tables:
    - Figure 15.1.2.1.6 and 15.1.2.1.7: Listing 15.3.6.2.5 and 15.3.6.2.10
    - Figure 15.1.2.1.8 and 15.1.2.1.9: Listing 15.3.6.2.6 and 15.3.6.2.11
- No figure shells are provided but will be generated during the tables/figures production.

15.1.2.2 Subjective Measurement Figures

Figure 15.1.2.2.1	Box Plot of the Responses to the Sensory Questionnaire by Product and Product Use (Pharmacodynamic Population)
Figure 15.1.2.2.2.1	Box Plot of the Responses to the modified Cigarette Evaluation Questionnaire by Product for *Ad Libitum* Use (Satisfaction) (Pharmacodynamic Population)
Figure 15.1.2.2.2.2	Box Plot of the Responses to the modified Cigarette Evaluation Questionnaire by Product for *Ad Libitum* Use (psychological reward) (Pharmacodynamic Population)
Figure 15.1.2.2.2.3	Box Plot of the Responses to the modified Cigarette Evaluation Questionnaire by Product for *Ad Libitum* Use (Aversion) (Pharmacodynamic Population)
Figure 15.1.2.2.2.4	Box Plot of the Responses to the modified Cigarette Evaluation Questionnaire by Product for *Ad Libitum* Use (Relief) (Pharmacodynamic Population)
Figure 15.1.2.2.3.1	VAS Craving Assessment versus Time by Product (Fixed Puffing) (Pharmacodynamic Population)
Figure 15.1.2.2.3.2	VAS Craving Assessment versus Time by Product (*Ad Libitum* Use) (Pharmacodynamic Population)
Figure 15.1.2.2.3.3	Box Plot of E60 of the VAS Craving Assessment by Product and Product Use (Pharmacodynamic Population)
Figure 15.1.2.2.3.4	Box Plot of Emax0-60 of the VAS Craving Assessment by Product and Product Use (Pharmacodynamic Population)
Figure 15.1.2.2.3.5	Box Plot of AUC of the VAS Craving Assessment by Product and Product Use (Pharmacodynamic Population)

15.1.2.3 Human Puffing Topography Figures

Figure 15.1.2.3.1.1	Box Plot of Human Puffing Topography Per-Puff Parameter (Puff Volume) by Product and Product Use (Pharmacodynamic Population)
Figure 15.1.2.3.1.2	Box Plot of Human Puffing Topography Per-Puff Parameter (Puff Duration) by Product and Product Use (Pharmacodynamic Population)

15.2 Summary Tables

15.2.1 Disposition and Background Data Summary Tables

Table 15.2.1.1 Summary of Disposition (Safety Population)

Table 15.2.1.2 Subject Using Study Product Status and Study Disposition (Safety Population)

Table 15.2.1.3 Demographic Summary (Safety Population)

Table 15.2.1.4 Smoking History and e-Cigarette Use Summary (Safety Population)

Table 15.2.1.5 Summary of Protocol Deviations

15.2.2 Primary Endpoints Summary Tables

15.2.2.1 Biomarkers of Exposure to Nicotine

Table 15.2.2.1.1 Summary of Plasma Nicotine PK Parameters Following *Ad Libitum* Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers

Table 15.2.2.1.2 Statistical Comparisons of Plasma Nicotine PK Parameters (C_{peak}, $C_{average}$ and $AUCb_{(0\text{-}4h)}$) Following *Ad Libitum* Regimen of P4M3 Variants Versus Subject Own e-Cigarette

Table 15.2.2.1.3 Wilcoxon Signed-Rank Test for t_{peak} Following *Ad Libitum* Regimen of P4M3 Variants Versus Subject Own e-Cigarette

Table 15.2.2.1.4 Summary of Plasma Nicotine PK Parameters Following Fixed Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers

Table 15.2.2.1.5 Geometric Mean Ratios (90% CIs) of the Nicotine Exposure-Normalized Plasma PK Parameters C_{max} and $AUC_{(0\text{-}4h)}$ Following Fixed Regimen Use for P4M3 Variants *versus* Subject's Own e-Cigarette

Table 15.2.2.1.6 Wilcoxon Signed-Rank Test for t_{max} Following Fixed Regimen Use for P4M3 Variants *versus* Subject's Own e-Cigarette

Table 15.2.2.1.7 Geometric Mean Ratios (90% CIs) of the Nicotine Exposure-Normalized Plasma PK Parameters C_{max} and $AUC_{(0\text{-}4h)}$ Following Fixed Regimen Use for P4M3-1.7%LA (Test) *versus* P4M3-1.7% (Reference)

15.2.3 Secondary Endpoints Summary Tables

15.2.3.1 Subjective Measurement Tables

15.2.6.4 Abnormal Laboratory Value Listing (each subject)

Table 15.2.6.4.1 Out-of-Range Values and Recheck Results – Clinical chemistry (Safety Population)

Table 15.2.6.4.2 Out-of-Range Values and Recheck Results – Hematology (Safety Population)

Table 15.2.6.4.3 Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)

Table 15.2.6.4.4 Clinically Significant Values and Recheck Results (Safety Population)

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

Table 15.2.6.5.1 Clinical Laboratory Summary and Change from Baseline – Clinical chemistry (Safety Population)

Table 15.2.6.5.2 Clinical Laboratory Shift from Baseline – Clinical chemistry (Safety Population)

Table 15.2.6.5.3 Clinical Laboratory Summary and Change from Baseline – Hematology (Safety Population)

Table 15.2.6.5.4 Clinical Laboratory Shift from Baseline – Hematology (Safety Population)

Table 15.2.6.5.5 Clinical Laboratory Summary and Change from Baseline – Urinalysis (Safety Population)

Table 15.2.6.5.6 Clinical Laboratory Shift from Baseline – Urinalysis (Safety Population)

Table 15.2.6.5.7 Vital Sign Summary for Screening, Admission, and Discharge (Safety Population)

Table 15.2.6.5.8 Vital Sign Summary for Days -1 through 4 and Change From Pre Product Use (Safety Population)

Table 15.2.6.5.9 12-Lead Electrocardiogram Summary and Change from Baseline (Safety Population)

Table 15.2.6.5.10 12-Lead Electrocardiogram Shift from Baseline (Safety Population)

Table 15.2.6.5.11 Spirometry Summary (Safety Population)

Table 15.2.6.5.12 Cough Assessment Summary (Safety Population)

Table 15.2.6.5.13 Concomitant Medication Summary (Safety Population)

15.3 Section 15.3 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.

15.3 Subject Data Listings and Figures

15.3.1 Subject Eligibility, Demographic Data, Baseline Characteristics

Listing 15.3.1.1.1	Inclusion Criteria
Listing 15.3.1.1.2	Inclusion Response (Safety Population)
Listing 15.3.1.2.1	Exclusion Criteria
Listing 15.3.1.2.2.1	Exclusion Response (I of II) (Safety Population)
Listing 15.3.1.2.2.2	Exclusion Response (II of II) (Safety Population)
Listing 15.3.1.3	Subject Eligibility (Safety Population)
Listing 15.3.1.4	Demographics (Safety Population)
Listing 15.3.1.5.1	Physical Examination (I of II) (Safety Population)
Listing 15.3.1.5.2	Physical Examination (II of II) (Safety Population)
Listing 15.3.1.5.3	Physical Examination Descriptions (Safety Population)
Listing 15.3.1.6	Medical and Surgical History (Safety Population)
Listing 15.3.1.7	Smoking History and e-Cigarette Use (Safety Population)
Listing 15.3.1.8	Subject Discontinuation (Safety Population)
Lisitng 15.3.1.9	Protocol Deviations

15.3.2 e-Cigarette Use

Listing 15.3.2.1	Randomization (Safety Population)
Listing 15.3.2.2.1	Fixed Puffing Product Use With HPT (I of II) (Safety Population)
Listing 15.3.2.2.2	Fixed Puffing Product Use With HPT (II of II) (Safety Population)
Listing 15.3.2.3.1	Ad Lib Product Use With HPT (I of II) (Safety Population)
Listing 15.3.2.3.2	Ad Lib Product Use With HPT (II of II) (Safety Population)

15.3.3 Listing of Biomarker Data

Listing 15.3.3.1	VAS Craving Assessment (Pharmacodynamic Population)
Listing 15.3.3.2	Sensory Questionnaire (Pharmacodynamic Population)
Listing 15.3.3.3.1	Adapted mCEQ Questionnaire (Original Score) (Pharmacodynamic Population)
Listing 15.3.3.3.2	Adapted mCEQ Questionnaire (Subscale Score) (Pharmacodynamic Population)

15.3.4 Safety Data Listings

15.3.4.1 Compliance and Concentration Data

Listing 15.3.4.1.1	Blood Draw Times (Safety Population)
Listing 15.3.4.1.2	Meal Times (Safety Population)
Listing 15.3.4.1.3	Prior and Concomitant Medications (Safety Population)
Listing 15.3.4.1.4	Concomitant Procedures (Safety Population)

15.3.4.2 Adverse Events Listings

Listing 15.3.4.2.1.1	Adverse Events (I of II) (Safety Population)
Listing 15.3.4.2.1.2	Adverse Events (II of II) (Safety Population)
Listing 15.3.4.2.2.1	Adverse Device Events (I of II) (Safety Population)
Listing 15.3.4.2.2.2	Adverse Device Events (II of II) (Safety Population)
Listing 15.3.4.2.3	Adverse Event Preferred Term Classification (Safety Population)

15.3.4.3 Listings of Individual Laboratory Measurements and Other Safety Observations

Listing 15.3.4.3.1.1	Clinical Laboratory Report - Clinical chemistry (Safety Population)
Listing 15.3.4.3.1.2	Clinical Laboratory Report - Hematology (Safety Population)
Listing 15.3.4.3.1.3	Clinical Laboratory Report - Urinalysis (Safety Population)
Listing 15.3.4.3.1.4	Clinical Laboratory Report – Urine Drug Screen (Safety Population)
Listing 15.3.4.3.1.5	Clinical Laboratory Report - Comments (Safety Population)
Listing 15.3.4.3.1.6	Breath Alcohol Screen (Safety Population)
Listing 15.3.4.3.1.7	Carbon Monoxide Breath Test (Safety Population)

Listing 15.3.4.3.1.8 Urine Drug Screen (Safety Population)
Listing 15.3.4.3.1.9 Urine Cotinine (Safety Population)
Listing 15.3.4.3.1.10 Urine Pregnancy (Safety Population)
Listing 15.3.4.3.1.11 CYP2A6 Activity (Trans-3'-Hydroxycotinine and Cotinine) (Safety Population)
Listing 15.3.4.3.2 Vital Signs (Safety Population)
Listing 15.3.4.3.3 12-Lead Electrocardiogram (Safety Population)
Listing 15.3.4.3.4 Pulmonary Function Test (Safety Population)
Listing 15.3.4.3.5 Cough Assessment (Safety Population)

15.3.5 Human Smoking Topography Assessment

Listing 15.3.5.1 HPT Parameters (Per Puff) (Pharmacodynamic Population)
Listing 15.3.5.2 HPT Parameters (Per Product) (Pharmacodynamic Population)

15.3.6 PK Figures and Listings

15.3.6.1 Figures

Figure 15.3.6.1.1 Individual Plasma Nicotine Concentration-Time Profiles Following *Ad Libitum* Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [Top: Linear-Linear; Bottom: Semi-Log]

Figure 15.3.6.1.2 Individual Plasma Nicotine Concentration-Time Profiles Following Fixed Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [Top: Linear-Linear; Bottom: Semi-Log]

Figure 15.3.6.1.3 Individual Background-Corrected Plasma Nicotine Concentration-Time Profiles Following *Ad Libitum* Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [Top: Linear-Linear; Bottom: Semi-Log]

Figure 15.3.6.1.4 Individual Background-Corrected Plasma Nicotine Concentration-Time Profiles Following Fixed Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [Top: Linear-Linear; Bottom: Semi-Log]

15.3.6.2 Listings

Biomarkers of Exposure to Nicotine

Listing 15.3.6.2.1	Listing of Individual Observed Plasma Nicotine Concentrations *versus* Time Following *Ad Libitum* Regimen P4M3 Use by No e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.2	Listing of Individual Observed Plasma Nicotine Concentrations *versus* Time Following Fixed Regimen P4M3 Use by No e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.3	Listing of Individual Background-Corrected Plasma Nicotine Concentrations *versus* Time Following *Ad Libitum* Regimen P4M3 Use by No e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.4	Listing of Individual Background-Corrected Plasma Nicotine Concentrations *versus* Time Following Fixed Regimen P4M3 Use by No e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.5	Individual Plasma Nicotine PK Parameters Following *Ad Libitum* Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.6	Individual Plasma Nicotine PK Parameters Following Fixed Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.7	Individual Background-Corrected Plasma Nicotine PK Parameters Following *Ad Libitum* Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.8	Individual Background-Corrected Plasma Nicotine PK Parameters Following Fixed Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers
Listing 15.3.6.2.9	Individual λ_z-related Plasma Nicotine PK Parameters Last P4M3 Product Use in Healthy Adult Smokers (Days 4 to 5)

Listing 15.3.6.2.10 Individual Theoretical Nicotine Exposure and Theoretical Rate of Nicotine Inhalation for *Ad Libitum* Regimen

Listing 15.3.6.2.11 Individual Theoretical Nicotine Exposure and Theoretical Rate of Nicotine Inhalation for Fixed Regimen

15.4 Statistical Output

15.4.1 Statistical Output for PK parameters

15.4.2 Statistical Output for Subjective Measures

15.4.3 Statistical Output for Human Puffing Topography

15.4 Appendices

The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

16.1.1 Protocol, Protocol Amendment and Notes to Files

16.1.2 Sample Case Report Form, Subject Questionnaire and Smoking Diary

16.1.3 List of IRBs and/or IECs, IRB/IEC Approvals, Sample Consent Forms, and Written Subject Information

16.1.4 List of Investigators and Other Important Participants and Descriptions of Qualifications and Research Facilities

16.1.5 List of Subjects Receiving Investigational Products from Specific Batches, where More Than One Batch Was Used

16.1.6 Randomization Scheme and Codes

16.1.7 Audit Certificates

16.1.8 Documentation of Statistical Methods

16.1.9 Bioanalytical Documentation

16.1.9.1 Standardization and Laboratory Reference Ranges

16. 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. These tables will be generated from the Celerion ADaM Version 2.1 data structure.

General TFL Specifications

1. Margins

   The general document margins for both A4 and US Letter (8.5”X11”) size paper are defined in Table 13.6.

Table 13.6: Document Margins for Paper Sizes - A4 and US Letter

Landscape Margins	inches	cm
Top	1.25	3.18
Bottom	1.00	2.54
Left	1.00	2.54
Right	1.00	2.54
Gutter (position = Left)	0	0
Portrait Margins		
Top	1.00	2.54
Bottom	1.00	2.54
Left	1.25	3.18
Right	1.00	2.54

   The header and footer information can appear within these margins as long as it is not within 3/8 of an inch of the edge of the page, because the text in this region may be lost upon printing or being bound.

2. General Font Size and Format

   In general, Arial 10 point font will be used for the content of TFLs; exceptionally 8-point font will be used when necessary to allow a large tables and/or listings to fit

within page limits. Font will be single spaced with 0 point spacing before and after the paragraph.

Title text will be Arial 12 point bold font with 0 point spacing before the title and 12 point spacing after the paragraph.

3. TFL Header/Footer Information

3.1 TFL Shells

The general header of on each page of the TFL shells will include the following information:

Sponsor: “Philip Morris International Research and Development”

Protocol ID as specified in the Protocol “P4M3-PK-02-US”

Status of the Document (i.e., Draft / Final)

Version Number and Date

The PMI R&D logo will only be reported in the first page of the document

3.2 Official TFL

The header for each TFL will include the following information:

Type of TFL (i.e., “Table”, “Figure”, or “Listing”)

The TFL number in the format, where the “X” is the numbering following the ICH E3 convention:

Figures = 15.1.X

Tables = 15.2.X

Listings = 15.3.X

The TFL text title, defining:

The endpoint(s) being presented

The presentation (e.g., summary, analysis, descriptive statistics)

The analysis population

The footer of each TFL will include the following information:

The page number / total number of pages (relative to the TFL)

Program name used to generate the TFL

Link to the source of the data being presented

Run date and run time (optional)

Status of the output: Dry run – Draft – Final Draft – Final (others as needed).

4. Abbreviations and Short Names

   Each TFL will be considered a stand-alone document and therefore all abbreviations used within the table will be spelled out in the footer of the table. Below are some of the standard abbreviations that are used in the TFLs.

   CV = Coefficient of Variation (in general, the CV will be used to indicate geometrical CV, if it refers to an arithmetic mean, it will be indicated in the footnotes)

   SD = Standard Deviation

   Min = Minimum

   Max = Maximum

   Mean (in general, the Mean will be used to indicate the arithmetic mean, if it refers to the geometrical mean, it will be indicated in the footnotes)

   Med = Median

   CI = Confidence Limit

   Q25 / Q75 = 25^{th} and 75^{th} Quartile

   BLOQ = Below Limit of Quantification

   N = the population total (it can be used for the overall population, subpopulation)

   n = the number of values reported for a specific endpoint at a specific time point

5. Data Presentation Formats, Precision and Rounding

   Dates are presented in the "day-month-year" (DDMONYYYY) format

   Times are presented in AM/PM format with preceding 0's (HH:MM AM)

   Continuous Variables having "x" decimal places, are summarized as follows:

   Minimum and Maximum → x decimal places

   Mean (geometrical and arithmetical), median, and confidence interval → x+1 decimal places

   Standard deviation → x+2 decimal places (unless otherwise stated)

   Rounding of standard deviations, CVs, and upper confidence limits will be rounded off upwards

   Rounding of lower confidence limits will be rounded off downward

   Percentages are expressed as 1 decimal place, except as follows

   Percentages = 100, will be presented as "100%" (no decimal places)

Percentages < 0.1, will be presented as "<0.1%"

Percentages for a 0 count, will not be presented

CV and ratio presented as a Percentage, will be presented to as 2 decimal places

P-values are expressed as 3 decimal places, except as follows

P-values < 0.001, will be presented as "<0.001"

P-values > 0.999, will be presented as ">0.999"

Categorical Variables will be presented as follows

If the total number of items/events is zero, data will be presented as 0

If the total number of items/events is zero, any further breakdown into sub-categories will not be presented

Missing values will be presented in a category = "Missing" unless another imputation method is specified in the SAP, in such cases the footnote may be used to provide the information on the imputation (e.g., 4 missing values were summarized as "Severe").

The denominator(s) used for all of the reported percentages is defined in the footnotes

Values that cannot be reported or summarized will be presented as "NA" and explained in the footnote

16.1 In-text Summary Tables Shells

In-text table 1 will be in the following format:

Table 1 Subject Disposition Summary (Safety Population)

	Sequence		
Disposition	**1**	**2**	**Overall**
Enrolled			X
Randomized	X (100%)	X (100%)	X (100%)
Completed	X (X%)	X (X%)	X (X%)
Discontinued Early	X (X%)	X (X%)	X (X%)
Reason 1	X (X%)	X (X%)	X (X%)
Reason 2	X (X%)	X (X%)	X (X%)

Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
Source: Table XX.X.X.
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_disp.sas DDMMMYYYY HH:MM

In-text table 2 will be in the following format:

Table 2 Demographic Summary (Safety Population)

		Sequence		
Trait	**Category/Statistics**	**1**	**2**	**Overall**
Sex	Male	X (XX%)	X (XX%)	X (XX%)
	Female	X (XX%)	X (XX%)	X (XX%)
Race	Asian	X (XX%)	X (XX%)	X (XX%)
	Black or African American	X (XX%)	X (XX%)	X (XX%)
	White	X (XX%)	X (XX%)	X (XX%)
Ethnicity	Not Hispanic or Latino	X (XX%)	X (XX%)	X (XX%)
	Hispanic or Latino	X (XX%)	X (XX%)	X (XX%)
Age (yrs)	n	X	X	X
	Mean	XX.X	XX.X	XX.X
	SD	XX.XX	XX.XX	XX.XX
	Minimum	XX	XX	XX
	Median	XX.X	XX.X	XX.X
	Maximum	XX	XX	XX
Weight (kg)	n	X	X	X
	Mean	XX.XX	XX.XX	XX.XX
	SD	XX.XXX	XX.XXX	XX.XXX
	Minimum	XX.X	XX.X	XX.X
	Median	XX.XX	XX.XX	XX.XX
	Maximum	XX.X	XX.X	XX.X
Height (cm)	n	X	X	X
	Mean	XXX.X	XXX.X	XXX.X
	SD	X.XX	X.XX	X.XX
	Minimum	XXX	XXX	XXX
	Median	XXX.X	XXX.X	XXX.X
	Maximum	XXX	XXX	XXX
BMI (kg/m²)	n	X	X	X
	Mean	XX.XXX	XX.XXX	XX.XXX
	SD	X.XXXX	X.XXXX	X.XXXX
	Minimum	XX.XX	XX.XX	XX.XX
	Median	XX.XXX	XX.XXX	XX.XXX
	Maximum	XX.XX	XX.XX	XX.XX

Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
SD = Standard deviation
BMI = Body mass index
Age is calculated at the time of informed consent.
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

In-text Tables 3 and 6 and Post-text Tables 15.2.2.1.1 and 15.2.2.1.4 will have the following format:

Table 3 Summary of Background-Corrected Plasma Nicotine PK Parameters Following *Ad Libitum* Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers

Pharmacokinetic Parameters	Subject Own e-Cigarette	P4M3-1.7%	P4M3-1.7%LA	P4M3-3%LA	P4M3-4%LA
Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param4 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]

cAUC(0-4h) and cCpeak values are presented as geometric mean and geometric CV%.
tpeak values are presented as median (min, max).
Other parameters are presented as arithmetic mean (± SD).
Source: Tables <XXXX> and <YYYY>
Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order and with following units:
  - Table 3: cCpeak <ng/mL>, tpeak <min>, cCtrough <ng/mL>, cCaverage <ng/mL>, and cAUC(0-4h) <ng*h/mL>
  - Table 6: cCmax <ng/mL>, tmax <min>, and cAUC(0-4h) <ng*h/mL>
  - Table 15.2.2.1.1: Cpeak <ng/mL>, tpeak <min>, Ctrough <ng/mL>, Caverage <ng/mL>, AUC(0-4h) <ng*h/mL>, and AUCb(0-4h) <ng*h/mL>
  - Table 15.2.2.1.4: Cmax <ng/mL>, tmax <min>, and AUC(0-4h) <ng*h/mL>

- n will be presented as an integer (with no decimal);
- See Section 14 for summary statistic presentation.
- Geom CV% will be presented to 1 decimal
- Source tables:
    - Table 3: Listing 15.3.6.2.7
    - Table 6: Listing 15.3.6.2.8
    - Table 15.2.2.1.1: Listing 15.3.6.2.5
    - Table 15.2.2.1.4: Listing 15.3.6.2.6

In-text Table 4, 7, and 9 and post-text Tables 15.2.2.1.2, 15.2.2.1.5 and 15.2.2.1.7 will have the following format:

Table 4 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameters (cC_{peak}, $cC_{average}$ and $cAUC_{(0-4h)}$) Following *Ad Libitum* Use of P4M3 Variants Versus Subject Own e-Cigarette

Parameter	Comparison	Geometric LSMs		GMR (%)	90% Confidence Intervals	Intra-subject CV%
		Test (n)	Reference (n)			
cC_{peak}	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
$cC_{average}$	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
$cAUC_{(0-4h)}$	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX

Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table XXXX

Notes for Generating the Actual Table:

Presentation of Data:

- The following PK parameters will be presented in the following order and with following units:
  - Table 4: cCpeak <ng/mL>, cCaverage <ng/mL>, and cAUC(0-4h) <ng*h/mL>
  - Table 7: cCmax <ng/mL> and cAUC(0-4h) <ng*h/mL>
  - Table 9: cCmax <ng/mL> and cAUC(0-4h) <ng*h/mL>
  - Table 15.2.2.1.2: Cpeak <ng/mL>, Caverage <ng/mL>, and AUCb(0-4h) <ng*h/mL>
  - Table 15.2.2.1.5: Cmax <ng/mL> and AUC(0-4h) <ng*h/mL>
  - Table 15.2.2.1.7: Cmax <ng/mL> and AUC(0-4h) <ng*h/mL>
- n will be presented as an integer (with no decimal);
- See Section 14 for summary statistic presentation.

In-Text Table 5, 8, 10 and post-text Table 15.2.2.1.3, 15.2.2.1.6, and 15.2.2.1.8 will have the following format:

Table 5 Wilcoxon Signed-Rank Test for Background-Corrected t_{peak} Following *Ad Libitum* Use of P4M3 Variants Versus Subject Own e-Cigarette

		-----Difference Test – Reference-----		
Parameter	**Comparison**	**Median**	**90% Confidence Interval**	**p-value**
tpeak	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX	X.XXXX - X.XXXX	X.XXXX
	P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX	X.XXXX - X.XXXX	X.XXXX
	P4M3-3%LA Vs Subject Own e-Cigarette	X.XX	X.XXXX - X.XXXX	X.XXXX
	P4M3-4%LA Vs Subject Own e-Cigarette	X.XX	X.XXXX - X.XXXX	X.XXXX

The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Rank test statistic.

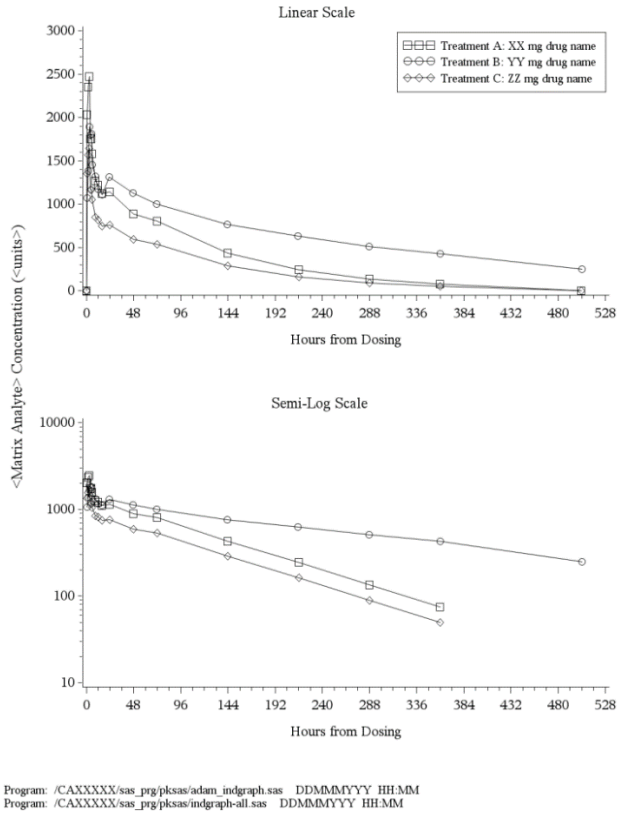
Notes for Generating the Actual Table:

Presentation of Data:

- See Section 14 for data presentation

In-text Figures 1 through 4, post-text Figures 15.1.1.1 through 15.1.1.4, and 15.3.6.1.1 through 15.3.6.1.4 will have the following format:

Figure 1 Background-Corrected Plasma Nicotine Mean (SD) Concentration-Time Profiles following *Ad Libitum* Regimen P4M3 use by e-Liquid Variant in Healthy Adult Smokers [Top Panel: Linear-Linear, Bottom Panel: Semi-Log]

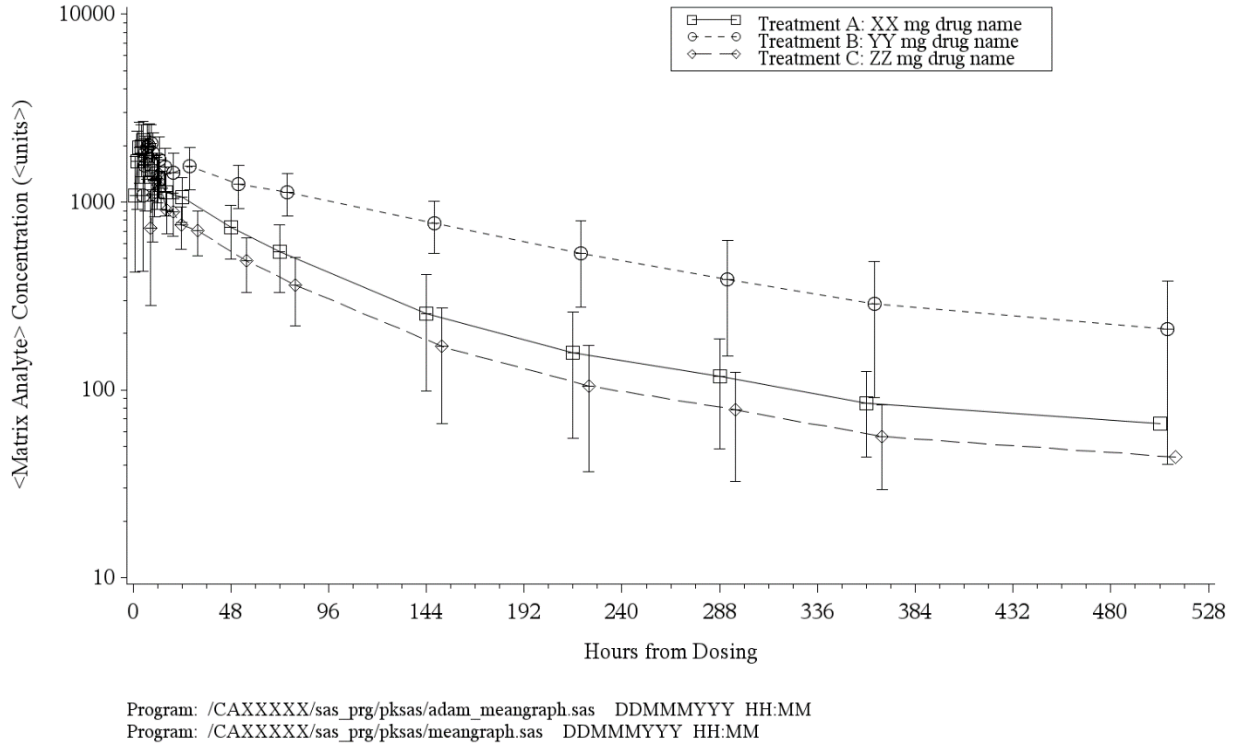


Notes for Generating the Actual Individual Figure:

- Legend will be "Subject Own e-Cigarette", "P4M3-1.7%", "P4M3-1.7%LA", "P4M3-3.3%LA", and "P4M3-4%LA"
- Y axis label will be "Plasma Nicotine Concentration (ng/mL)"
- X axis label will be "Time (minute)"
- Figure 2, 4, 15.1.1.2, and 15.1.1.4 will be truncated at 1 hour
- Source tables:
    - Figures 1 and 2: Listing 15.3.6.2.3
    - Figures 3 and 4: Listing 15.3.6.2.4
    - Figures 15.1.1.1 and 15.1.1.2: Listing 15.3.6.2.1
    - Figures 15.1.1.3 and 15.1.1.4: Listing 15.3.6.2.2
    - Figure 15.3.6.1.1: Listing 15.3.6.2.1
    - Figure 15.3.6.1.2: Listing 15.3.6.2.2
    - Figure 15.3.6.1.3: Listing 15.3.6.2.3
    - Figure 15.3.6.1.4: Listing 15.3.6.2.4

In-text Figure 5 and post-text Figure 15.1.1.5 will have the following format:

Figure 5 Background-Corrected Semi-Log Plasma Nicotine Mean (SD) Concentration-Time Profile after the Last *Ad Libitum* P4M3-4%LA Use on Day 4



Notes for Generating the Actual Individual Figure:

- Y axis label will be "Plasma Nicotine Concentration (ng/mL)"
- X axis label will be "Time (minute)"
- Source table:
    - Figure 5: Listing 15.3.6.2.3
    - Figure 15.1.1.5: Listing 15.3.6.2.1

Listings 15.3.6.2.1 through 15.3.6.2.4 will have the following format:

Page 1 of X

Listing 15.3.6.2.1 Listing of Individual Observed Plasma Nicotine Concentrations *versus* Time Following *Ad Libitum* Regimen P4M3 Use by No e-Liquid Variant in Healthy Adult Smokers

Subject Number	Product Sequence	Study Day	Blood Sample Times (minutes) From Start of Product Use: Pre-use	XX	XX	XX	XX	XX	XX	XX
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	XX
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	XX
XX	XXXXXX	X	XX	XX	XX	XX	XX	XX	XX	XX
n			X	X	X	X	X	X	X	X
Mean			X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
SD			X.XX	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	XX.X
SEM			X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
Minimum			XX	XX	XX	XX	XX	XX	XX	XX
Median			X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
Maximum			XX	XX	XX	XX	XX	XX	XX	XX
Geo. Mean			X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
Geo. CV%			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

For the calculation of summary statistics, values that are below the limit of quantification (BLQ) of <XX> are treated as <0> before the first quantifiable concentration and as missing elsewhere.
. = Value missing or not reportable.
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Notes for Generating the Actual Tables:

- Please use CPConc1 template
- The following footnote will only be included in the uncorrected tables: < Concentration values that were below the limit of quantification (BLQ) of X.X ng/mL were set to missing for the calculation of the descriptive statistics.>
- The following footnote will only be included in the baseline corrected tables: <After baseline correction, any negative values were set to missing except individual plasma concentration values between the start of product use and the first time point above LLOQ (i.e. during lag-time) which were set to 0.>
- Footnote to include under the table, as appropriate: . = Value missing due to <no sample collected>.
- Sample times:
    - Listings 15.3.6.2.1 and 15.3.6.2.3: Pre-use and 10, 20, 30, 40, 60, 120, and 240 minutes following the start of each product use.
    - Listings 15.3.6.2.2 and 15.3.6.2.4: Pre-use and 2, 4, 7, 10, 15, 30, 60, 120, 240 minutes following the start of each product use.
- Concentrations will be presented to the same precision as in the bio data.
- Descriptive statistics presentation with respect to the precision of the bio data: n = integer; Mean and Median +1; SD and SEM +2, Min and Max +0, CV% to 1 decimal.

Listings 15.3.6.2.5 through 15.3.6.2.8 will have the following format:

Page 1 of X

Listing 15.3.6.2.5 Individual Plasma Nicotine PK Parameters Following *Ad Libitum* Regimen P4M3 Use by e-Liquid Variant in Healthy Adult Smokers

			Parameters				
Subject Number	Product Sequence	Study Day	Parm 1 <unit>	Parm 2 <unit>	Parm 3 <unit>	Parm 4 <unit>	Parm X <unit>
XX	XXX	X	X.XX	X.XX	X.XX	X.XX	X.XX
XX	XXX	X	X.XX	X.XX	X.XX	X.XX	X.XX
XX	XXX	X	X.XX	X.XX	X.XX	X.XX	X.XX
n			X	X	X	X	X
Mean			X.X	X.X	X.X	X.X	X.X
SD			X.XX	X.XX	X.XX	X.XX	X.XX
CV(%)			XX.X	XX.X	XX.X	XX.X	XX.X
SEM			X.XX	X.XX	X.XX	X.XX	X.XX
Minimum			XX	XX	XX	XX	XX
Median			X.X	X.X	X.X	X.X	X.X
Maximum			XX	XX	XX	XX	XX
Geo. Mean			X.X	X.X	X.X	.	.
Geo. CV%			XX.X	XX.X	XX.X	.	.

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

Notes for Generating the Actual Tables:

- Please use the CPPar1 template.
- Footnote to include under the table, as appropriate: <. = Parameter value missing or not calculable>

- PK parameters will be presented in the following order with following units:
    - Listings 15.3.6.2.5: Cpeak <ng/mL>, tpeak <min>, Ctrough <ng/mL>, Caverage <ng/mL>, AUC(0-4h) <ng*h/mL>, and AUCb(0-4h) <ng*h/mL>
    - Listings 15.3.6.2.6: Cmax <ng/mL>, tmax <min>, and AUC(0-4h) <ng*h/mL>
    - Listings 15.3.6.2.7: cCpeak <ng/mL>, tpeak <min>, cCtrough <ng/mL>, cCaverage <ng/mL>, and cAUC(0-4h) <ng*h/mL>
    - Listings 15.3.6.2.8: cCmax <ng/mL>, tmax <min>, and cAUC(0-4h) <ng*h/mL>
- Individual exposure based PK parameters will be reported with 3 significant digits.
- Individual time based PK parameters will be reported with 2 decimals.
- Descriptive statistics presentation with respect to the precision of the individual PK parameters: n = integer; Mean/Median/Geo. Mean +1; SD and SEM +2, Min and Max +0, CV% and Geo. CV% to 1 decimal
- Geo. Mean and Geo. CV% will be calculated only for exposure based PK parameters only.

Listing 15.3.6.2.9 will have the following format:

Page 1 of X

Listing 15.3.6.2.9 Individual λ_z-related Plasma Nicotine PK Parameters Last P4M3 Product Use in Healthy Adult Smokers (Days 4 to 5)

Subject	Subject Own e-Cigarette					P4M3-1.7%				
Number	Interval	R^2	N	λz	t½z	Interval	R^2	N	λz	t½z
XX	X.X - XX.X	X.XXX	X	X.XXX	X.XX	X.X - XX.X	X.XXX	X	X.XXX	X.XX
XX	X.X - XX.X	X.XXX	X	X.XXX	X.XX	X.X - XX.X	X.XXX	X	X.XXX	X.XX
XX	X.X - XX.X	X.XXX	X	X.XXX	X.XX	X.X - XX.X	X.XXX	X	X.XXX	X.XX

Note: R2 = coefficient of determination of the linear regression
N = Number of points used in kel calculation
. = Parameter value missing or not calculable
Program: /CAXXXXX/sas_prg/pksas PROGRAMNAME.SAS DDMMMYYYY HH:MM

Notes for Generating the Actual Tables:

- Please use the CPKel1 template.
- Add column in for 'Product Sequence' and 'Study Day
- Additional columns will be added to include all 5 products
- Interval start and stop times will be presented to 1 decimal
- R^2 will be presented to 3 decimals
- n will be presented as an integer (with no decimal)
- λ_z will be presented to 3 decimals
- $t_{½z}$ will be presented to 2 decimals

Listings 15.3.6.2.10 and 15.3.6.2.11 will have the following format:

Listing 15.3.6.2.10 Individual Theoretical Nicotine Exposure and Theoretical Rate of Nicotine Inhalation for *Ad Libitum* Regimen

Subject Number	Product	Total Puff Volume (mL)	Nicotine (µg/mL)	Theoretical Nicotine Exposure (µg)	Total Puff Duration (s)	Theoretical Rate of Nicotine Inhalation [R_0] (µg/s)
XX	P4M3-1.7%	XX.X	XX.X	XX.X	XX	XX.X
	P4M3-1.7%LA	XX.X	XX.X	XX.X	XX	XX.X
	P4M3-3%LA	XX.X	XX.X	XX.X	XX	XX.X
	P4M3-4%LA	XX.X	XX.X	XX.X	XX	XX.X

Source: Table XX.X.X.X
Program: /CAXXXXX/sas_prg/pksas/intexttest/programname.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Tables:

- See Section 11.3 under Graphical Exploratory Analysis for details for the calculations of 'Nicotine', 'Theoretical Nicotine Exposure', and 'Theoretical Rate of Nicotine Inhalation'.
- 'Total Puff Volume' and 'Total Puff Duration' are from the HPT data in Listing 15.3.5.2

In-text Table 11 will be in the following format:

Table 11 Summary of the Responses to the Sensory Questionnaire (Pharmacodynamic Population)

Product	Subject Own e-Cigarette		P4M3-1.7%		P4M3-1.7%LA		P4M3-3%LA		P4M3-4%LA	
Product Use	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx
1. How much did you like the puffs you took?	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
2. How harsh were the puffs you took?	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
3. How similar to your own brand were the puffs?	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
4. Strength of puffs on tongue?	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
5. Strength of puffs in nose?)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
6. Strength of puffs in back of mouth & throat?	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
7. Strength of puffs in windpipe?	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
8. Strength of puffs in chest?	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)

Data are presented as arithmetic mean (± SD).
SD = Standard deviation
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/pksas/intexttest/programname.sas DDMMMYYYY HH:MM

In-text Table 12 will be in the following format:

Table 12 Statistical Comparisons of the Responses to the Sensory Questionnaire (Pharmacodynamic Population)

Question	Product Use	LS Means					
		Comparison	Test (n)	Reference (n)	LS Means Difference (Test - Reference)	90% Confidence Intervals	p-Value
1. How much did you like the puffs you took?	Fixed Puff	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX

n = Number of observation used in the analysis
Least-squares means (LS Means) are calculated from the ANOVA.
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/pksas/pd/adam_intext_pd_statsmixed.sas DDMMMYYYY HH:MM

Programmer Note: All questions in the SQ questionnaire will be included in the table.

In-text Table 13 will be in the following format:

Table 13 Summary of the Responses to the Adapted modified Cigarette Evaluation Questionnaire (Pharmacodynamic Population)

Product	Subject Own e-Cigarette	P4M3-1.7%	P4M3-1.7%LA	P4M3-3%LA	P4M3-4%LA
Product Use	**Ad Lib Use** N=xx	**Ad Lib Use** N=xx	**Ad Lib Use** N=xx	**Ad Lib Use** N=xx	**Ad Lib Use** N=xx
	Subscale Score				
Smoking satisfaction	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)
Psychological reward	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)
Aversion	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)
Enjoyment of the sensory sensation	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)
Craving reduction	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)	X.X (XX.X)

Data are presented as arithmetic mean (± SD).
SD = Standard Deviation
Source: Tables XX.X.X and XX.X.X
Program: /CAXXXXX/sas_prg/pksas/intexttest/programname.sas DDMMMYYYY HH:MM

In-text Table 14 will be in the following format:

Table 14 Statistical Comparisons of the Responses to the Adapted modified Cigarette Evaluation Questionnaire (Pharmacodynamic Population)

Subscale	Product Use	Comparison	LS Means		LS Means Difference (Test - Reference)	90% Confidence Intervals	p-Value
			Test (n)	Reference (n)			
Smoking Satisfaction	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
Psychological reward	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
Aversion	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
Enjoyment of respiratory tract sensation	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
Craving reduction	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX

Subscale	Product Use	Comparison	LS Means Test (n)	LS Means Reference (n)	LS Means Difference (Test - Reference)	90% Confidence Intervals	p-Value
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX

n = Number of observation used in the analysis
Least-squares means (LS Means) are calculated from the ANOVA.
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/pksas/pd/adam_intext_pd_statsmixed.sas DDMMMYYYY HH:MM

In-text Table 15 will be in the following format:

Table 15 Summary of the VAS Craving Assessment (Pharmacodynamic Population)

Product	Subject Own e-Cigarette		P4M3-1.7%		P4M3-1.7%LA		P4M3-3%LA		P4M3-4%LA	
Product Use	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx
E_{60}	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
$Emax_{0-60}$	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)
AUC_{0-60}	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)	X.X (X.XX)	X.X (XX.X)

Data are presented as arithmetic mean (± SD).
SD = Standard deviation
E_{60} = VAS craving assessment score at 60 minutes after the start of product administration
$Emax_{0-60}$ = Maximum VAS craving assessment score between 0 to 60 minutes of product administration
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/pksas/intexttest/programname.sas DDMMMYYYY HH:MM

In-text Table 16 will be in the following format:

Table 16 Statistical Comparisons of the VAS Craving Assessment (Pharmacodynamic Population)

Parameter	Product Use	Comparison	LS Means		LS Means Difference (Test - Reference)	90% Confidence Intervals	p-Value
			Test (n)	Reference (n)			
E_{60}	Fixed Puff	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX

n = Number of observation used in the analysis
Least-squares means (LS Means) are calculated from the ANOVA.
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/pksas/pd/adam_intext_pd_statsmixed.sas DDMMMYYYY HH:MM

Programmer Note: All parameters (E60, Emax0-60, and AUC0-60) will be included in the table.

In-text Tables 17 and 18 will be in the following format:

Table 17 Summary of Human Puffing Topography Per-Puff Parameters (Pharmacodynamic Population)

Product	Subject's Own e-Cigarette		P4M3-1.7%		P4M3-1.7%LA		P4M3-3%LA		P4M3-4%LA	
Product Use	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx	Fixed Puffing N=xx	Ad Lib Use N=xx
Puff volume (mL)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)
Puff duration (s)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)
Average flow (mL/s)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)	XX.XXX (XX.XX)
Peak flow (mL/s)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)
Inter puff interval (s)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)
Sum of Inter puff interval and duration (s)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)	XX.XXX (XX.XX)	XXX.XXX (XX.X)
Work (mJ)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)	XXXX.XX X (XX.XX)
Average pressure drop (mmWG)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)
Peak pressure drop (mmWG)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)	XXX.XXX (XX.XX)
Average resistance (mmWG/mL/s)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)
Peak resistance (mmWG/mL/s)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)	X.XXX (XX.XX)

Number of peaks	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)	XX (XX.XX)

Data are presented as Geometric mean (Geometric CV%).
CV% = Coefficient of variance
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/pksas/intexttest/programname.sas DDMMMYYYY HH:MM

Programmer Note: Check the actual data for the decimal points for each parameter.

In-text table 19 will be in the following format:

Table 19 Adverse Event Frequency by Product - Number of Subjects Reporting the Event (% of Subjects Used Study Product) (Safety Population)

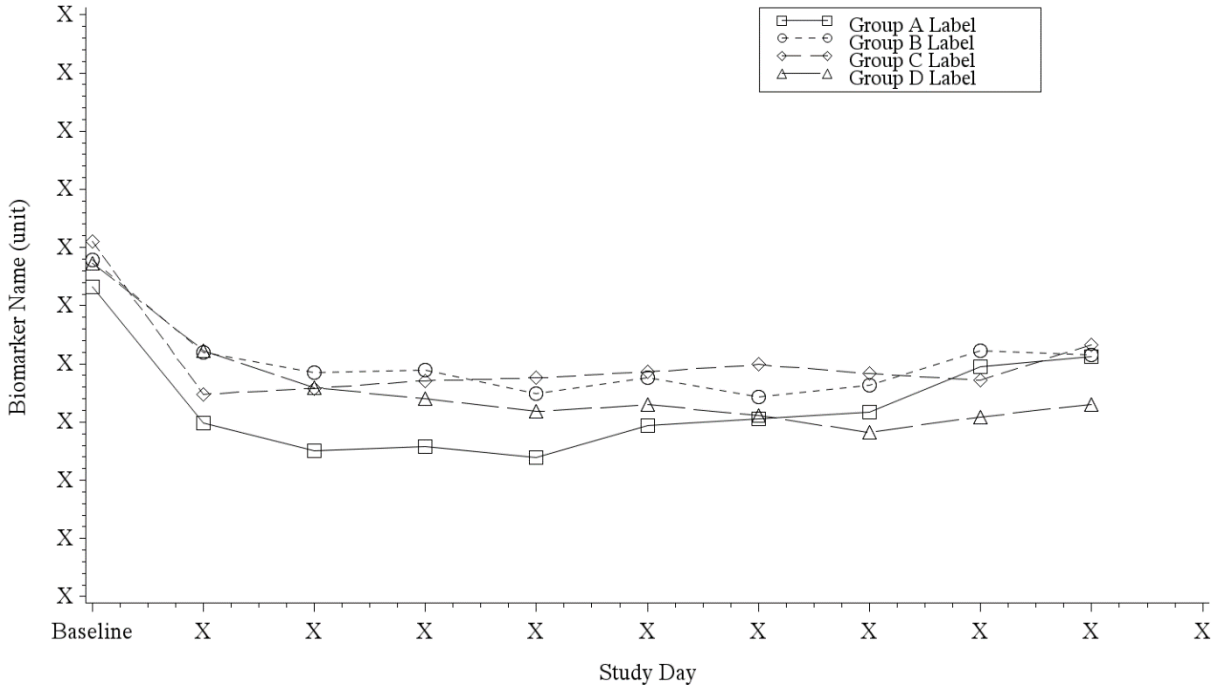
	Admission	Baseline	Study Product				
Adverse Events*	**P4M3-1.7%**	**Subject's Own e-cigarette**	**P4M3-1.7%**	**P4M3-1.7%LA**	**P4M3-3 %LA**	**P4M3-4%LA**	**Overall**
Number of Subjects Used Study Product	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)
Number of Subjects With Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
General disorders and administration site conditions	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Vessel puncture site pain	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Vessel puncture site reaction	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)

*Adverse events are classified according to MedDRA® Version 20.0
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_ae.sas DDMMMYYYY HH:MM

16.2 Figures Shells

In-text Figures 15, 16 and post-text Figures15.1.2.2.3.1 and 15.1.2.2.3.2 will be in the following format:

Figure X.X.X
VAS Craving Assessment versus Time by Product (Fixed puffing)
(Pharmacodynamic Population)

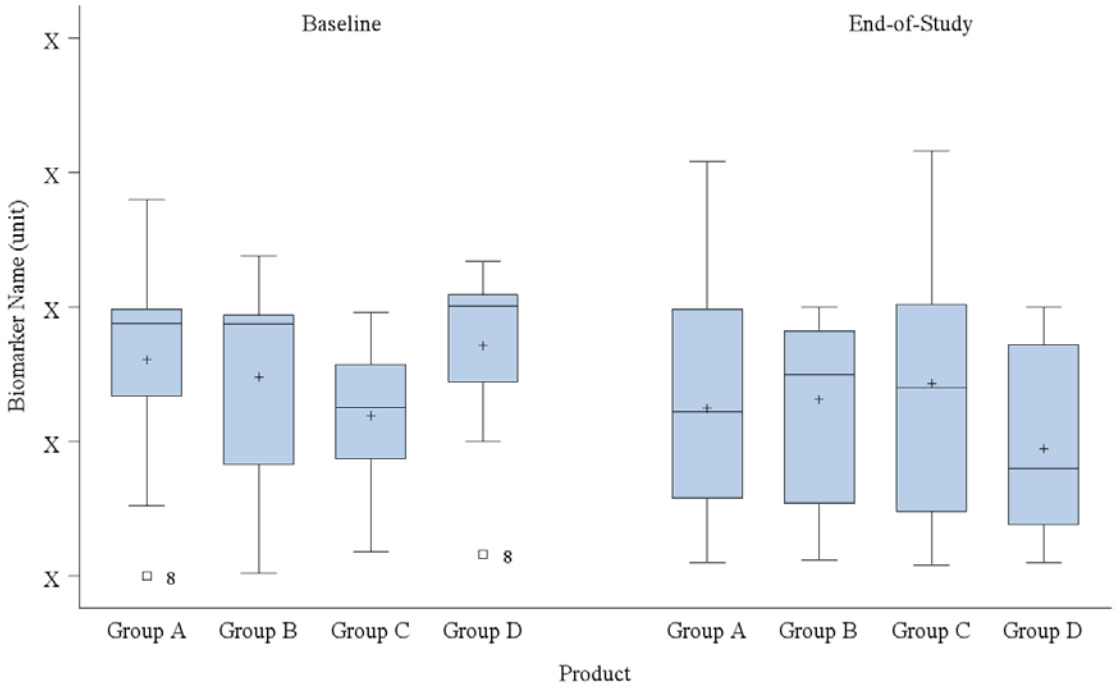


Program: CAXXXXX/XXX/XXX PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: The x-axis will be time point (minutes) and y-axis is the mean craving score. There will be 5 lines in the graph which are corresponding to the 5 study products (Subject Own e-cigarette and four P4M3 products).

The box plot will be in the following format.

Figure X.X.X.X
Box Plot of Name (unit) by Product and Product Use



The upper and lower whiskers of the boxplot represent, respectively, the largest and smallest observed values within 1.5 × the interquartile range (IQR) from the upper and lower quartiles (Q3 and Q1). Values greater or smaller than the bounds represented by these whiskers are identified as extreme values with the corresponding subject number.

Program: CAXXXXX/XXX/XXX PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: The x-axis will be products and y-axis is the measurements. There will be 5 products in each panel which are corresponding to the 5 study products (Subject Own e-cigarette and four P4M3 products) and 2 panels (for fixed puffing and ad lib use).

16.3 Section 15.2 Summary Tables Shells

Refer to Section 14 (3.1 and 3.2) for header and footer instructions.

Table 15.2.1.1 will have the following format:

Table 15.2.1.1 Summary of Disposition (Safety Population)

	Product Sequence		
Category	**1**	**2**	**Overall**
Enrolled			XX
Randomized	XX (100%)	XX (100%)	XX (100%)
Completed	XX (XX%)	XX (XX%)	XX (XX%)
Discontinued Early	X (XX%)	X (XX%)	X (XX%)
<Reason>	X (XX%)	X (XX%)	X (XX%)

Note: Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
Program: /AAXXXXX/ECR/sas_prg/stsas/tab prog_name.sas DDMMMYYYY HH:MM

Table 15.2.1.2 will have the following format:

Table 15.2.1.2 Subject Using Study Product Status and Study Disposition (Safety Population)

Subject Number	Sequence	Product Administered/Completed				Study Completion	
		P4M3-1.7%	P4M3-1.7%LA	P4M3-3%LA	P4M3-4%LA	Status	Date
X	X	Yes	Yes	Yes	No	Terminated Study Prematurely	DDMMMYYYY
X	X	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	X	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	X	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
		------	------	------	------		
		XX	XX	XX	XX		

Note: Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
Program: /CAXXXXX/sas_prg/stsas/tab cdash_tbldisp2.sas DDMMMYYYY HH:MM

Table 15.2.1.3 will have the following format:

Table 15.2.1.3 Demographic Summary (Safety Population)

		Sequence		
		1	2	
Trait				**Overall**
Sex	Male	X(XX.X%)	X(XX.X%)	X(XX.X%)
	Female	X(XX.X%)	X(XX.X%)	X(XX.X%)
Race	XXXXXXXXXX	X(XX.X%)	X(XX.X%)	X(XX.X%)
	XXXXX	X(XX.X%)	X(XX.X%)	X(XX.X%)
	XXXXX	X(XX.X%)	X(XX.X%)	X(XX.X%)
Ethnicity	Hispanic or Latino	X(XX.X%)	X(XX.X%)	X(XX.X%)
	Not Hispanic or Latino	X(XX.X%)	X(XX.X%)	X(XX.X%)
Age (yrs)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX

Note: Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
SD = Standard deviation
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 summary table.

Table 15.2.1.4 will have the following format:

Table 15.2.1.4 Smoking History and e-Cigarette Use Summary (Safety Population)

		Sequence		
Question	**Answer**	**1**	**2**	**Overall**
1. Have you ever smoked 100 cigarettes or more in your life?	Yes	X(XX.X%)	X(XX.X%)	X(XX.X%)
	No	X(XX.X%)	X(XX.X%)	X(XX.X%)
2. What is your current cigarette smoking behavior (including hand-rolled cigarettes)?	Daily smoker	X(XX.X%)	X(XX.X%)	X(XX.X%)
	Occasional smoker	X(XX.X%)	X(XX.X%)	X(XX.X%)
	Ex-smoker of cigarettes	X(XX.X%)	X(XX.X%)	X(XX.X%)
	Non-smoker of cigarettes	X(XX.X%)	X(XX.X%)	X(XX.X%)
3. If you are an ex-smoker of cigarettes: For how long have you quit now? (yrs)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX

Note: Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
SD = Standard deviation
Program: /CAXXXXX/sas_prg/stsas/tab cdash_demsum.sas DDMMMYYYY HH:MM

Programmer Note: All questions in the smoking history and e-cigarette use will be included in the summary table.

Table 15.2.3.1.1 will have the following format:

Table 15.2.3.1.1 Summary Statistics of the Responses to Sensory Questionnaire (Pharmacodynamic Population)

Question	Product Use	Statistics	Subject Own e-Cigarette	P4M3-1.7%	P4M3-1.7%LA	P4M3-3 %LA	P4M3-4%LA
1. How much did you like the puffs you took?	Fixed Puffing	n	X	X	X	X	X
		n missing	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX
	Ad Lib Use	n	X	X	X	X	X
		n missing	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX

Note: SD = Standard deviation
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All questions in the SQ questionnaire will be included in the summary table.

Table 15.2.3.1.2.1 will have the following format:

Table 15.2.3.1.2.1 Statistical Summary of the Responses to Sensory Questionnaire (Pharmacodynamic Population)

Question	Product Use	Product	n	LS Mean	XX% Confidence Intervals	p-Value
1. How much did you like the puffs you took?	Fixed Puffing	Subject Own e-Cigarette	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
	Ad Lib Use	Subject Own e-Cigarette	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA	X	X.XX	XX.XX – XXX.XX	X.XXX

Note: LS = Least-square
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All questions in the SQ questionnaire will be included in the table.

Table 15.2.3.1.2.2 will have the following format:

Table 15.2.3.1.2.2 Statistical Comparisons of the Responses to Sensory Questionnaire (Pharmacodynamic Population)

Question	Product Use	Comparison	LS Means Test (n)	LS Means Reference (n)	LS Mean Difference (Test - Reference)	XX% Confidence Interval	p-Value
1.XXXXXX	Fixed Puffing	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X XX (X)	X.XX (X)	XXX XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X XX (X)	X.XX (X)	XXX XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX

Test = The first product in the comparison
Reference = The second product in the comparison
n = Number of observation used in the analysis
Least-squares means (LS Means) are calculated from the ANOVA.
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All questions in the SQ questionnaire will be included in the summary table.

Table 15.2.3.1.3 will have the following format:

Table 15.2.3.1.3 Summary Statistics of the Responses to the modified Cigarette Evaluation Questionnaire (Subscale Score) (Pharmacodynamic Population)

Question	Product Use	Statistics	Subject Own e-Cigarette	P4M3-1.7%	P4M3-1.7%LA	P4M3-3 %LA	P4M3-4%LA
Satisfaction	Ad Lib Use	n	X	X	X	X	X
		n missing	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX

Note: SD = Standard deviation
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All subscale score for the mCEQ questionnaire will be included in the summary table.

Table 15.2.3.1.4.1 will have the following format:

Table 15.2.3.1.4.1 Statistical Summary of the Responses to the Adapted modified Cigarette Evaluation Questionnaire (Subscale Score) (Pharmacodynamic Population)

Question	Product Use	Product	n	LS Mean	XX% Confidence Intervals	p-Value
Satisfaction	Ad Lib Use	Subject Own e-Cigarette	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA	X	X.XX	XX.XX – XXX.XX	X XXX
		P4M3-3%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA	X	X.XX	XX.XX – XXX.XX	X XXX

Note: LS = Least-square
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All subscale score for the mCEQ questionnaire will be included in the summary table.

Table 15.2.3.1.4.2 will have the following format:

Table 15.2.3.1.4.2 Statistical Summary of the Responses to the modified Cigarette Evaluation Questionnaire (Subscale Score) (Pharmacodynamic Population)

Question	Product Use	Comparison	—— LS Means —— Test (n)	Reference (n)	LS Mean Difference (Test - Reference)	XX% Confidence Interval	p-Value
Satisfaction	Ad Lib Use	P4M3-1.7% Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA Vs Subject Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX

Test = The first product in the comparison
Reference = The second product in the comparison
n = Number of observation used in the analysis
Least-squares means (LS Means) are calculated from the ANOVA.
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All subscale score in the mCEQ questionnaire will be included in the summary table.

Tables 15.2.3.1.5.1 and 15.2.3.1.5.2 will have the following format:

Table 15.2.3.1.5.1 Summary Statistics of the VAS Craving Assessment by Time Point (Fixed Puffing) (Pharmacodynamic Population)

		Product Use Sample Times (minute)							
Product	**Statistics**	**Pre-use**	**4**	**10**	**15**	**30**	**60**	**120**	**240**
Subject's Own e-Cigarette	n	X	X	X	X	X	X	X	X
	n missing	X	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
	Minimum	XX	XX	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XXX	XX	XXX	XX	XXX	XXX	XX
P4M3-1.7%	n	X	X	X	X	X	X	X	X
	n missing	X	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
	Minimum	XX	XX	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XXX	XX	XXX	XX	XXX	XXX	XX

Note: SD = Standard deviation
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All products will be included in the summary table.

Tables 15.2.3.1.5.3 and 15.2.3.1.5.4 will have the following format:

Table 15.2.3.1.5.3 Summary Statistics of the VAS Craving Assessment by Time Point (Ad Lib Use) (Pharmacodynamic Population)

		Product Use Sample Times (minute)							
Product	**Statistics**	**Pre-use**	**10**	**20**	**30**	**40**	**60**	**120**	**240**
Subject's Own	n	X	X	X	X	X	X	X	X
e-Cigarette	n missing	X	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
	Minimum	XX	XX	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XXX	XX	XXX	XX	XXX	XXX	XX
P4M3-1.7%	n	X	X	X	X	X	X	X	X
	n missing	X	X	X	X	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
	Minimum	XX	XX	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XXX	XX	XXX	XX	XXX	XXX	XX

Note: SD = Standard deviation

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

Tables 15.2.3.1.6.1 and 15.2.3.1.6.3 will have the following format:

Table 15.2.3.1.6.1 Statistical Summary of the VAS Craving Assessment by Time Point (Fixed Puffing) (Pharmacodynamic Population)

Product	Time Point	n	LS Mean	XX% Confidence Intervals	p-Value
Subject's Own e-Cigarette	Pre-use	X	X.XX	XX.XX – XXX.XX	X.XXX
	4 Minutes	X	X.XX	XX.XX – XXX.XX	X.XXX
	10 Minutes	X	X.XX	XX.XX – XXX.XX	X.XXX
	15 Minutes	X	X.XX	XX.XX – XXX.XX	X.XXX

Note: LS = Least-square
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All time points and products will be included in the table.

Tables 15.2.3.1.6.2 and 15.2.3.1.6.4 will have the following format:

Table 15.2.3.1.6.2 Statistical Comparisons of the VAS Craving Assessment by Time Point (Fixed Puffing) (Pharmacodynamic Population)

Time Point	Comparison	LS Means		LS Mean Difference (Test - Reference)	XX% Confidence Interval	p-Value
		Test (n)	Reference (n)			
Pre-Use	P4M3-1.7% Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-1.7%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-3%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-4%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
4 Minutes	P4M3-1.7% Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-1.7%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-3%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-4%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
10 Minutes	P4M3-1.7% Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-1.7%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-3%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	P4M3-4%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX

Test = The first product in the comparison
Reference = The second product in the comparison
n = Number of observation used in the analysis
Least-squares means (LS Means) are calculated from the ANOVA.
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All time points will be included in the table.

Table 15.2.3.1.7 will have the following format:

Table 15.2.3.1.7 Summary Statistics of the VAS Craving Assessment Parameters (Pharmacodynamic Population)

Parameter	Product Use	Statistics	Subject's Own e-Cigarette	P4M3-1.7%	P4M3-1.7%LA	P4M3-3 %LA	P4M3-4%LA
Emax0-4h	Fixed Puffing	n	X	X	X	X	X
		n missing	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX
	Ad Lib Use	n	X	X	X	X	X
		n missing	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX

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

Programmer Note: All parameters [Emax(0-4h), AUC(0-4h)] will be included in the summary table.

Table 15.2.3.1.8.1 will have the following format:

Table 15.2.3.1.8.1 Statistical Summary of the VAS Craving Assessments (Pharmacodynamic Population)

Parameter	Product Use	Product	n	LS Mean	XX% Confidence Intervals	p-Value
Emax0-4h	Fixed Puffing	Subject's Own e-Cigarette	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
	Ad Lib Use	Subject's Own e-Cigarette	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA	X	X.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA	X	X.XX	XX.XX – XXX.XX	X.XXX

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

Programmer Note: All parameters [Emax(0-4h), AUC(0-4h)] will be included in the table.

Table 15.2.3.1.8.2 will have the following format:

Table 15.2.3.1.8.2 Statistical Comparisons of the VAS Craving Assessments (Pharmacodynamic Population)

Parameter	Product Use	Comparison	LS Means Test (n)	LS Means Reference (n)	LS Mean Difference (Test - Reference)	XX% Confidence Interval	p-Value
Emax0-4h	Fixed Puffing	P4M3-1.7% Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
	Ad Lib Use	P4M3-1.7% Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-1.7%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-3%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX
		P4M3-4%LA Vs Subject's Own e-Cigarette	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXX

Test = The first product in the comparison
Reference = The second product in the comparison
n = Number of observation used in the analysis
Least-squares means (LS Means) are calculated from the ANOVA.
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM

Programmer Note: All parameters in the VAS Craving will be included in the table.

Tables 15.2.3.2.1and 15.2.3.2.2 will have the following format:

Table 15.2.3.2.1 Summary Statistics of Human Puffing Topography Per-Puff Parameters (Pharmacodynamic Population)

Parameter (unit)	Product Use	Statistics	Subject's Own e-Cigarette	P4M3-1.7%	P4M3-1.7%LA	P4M3-3 %LA	P4M3-4%LA
XXXXXXXXXX(XX)	Fixed Puffing	n	X	X	X	X	X
		n missing	X	X	X	X	X
		Mean	X.X	X.X	X X	X.X	X.X
		SD	X XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX
		Geom. Mean	X.X	X.X	X.X	X.X	X.X
		Geom. CV%	X.X	X.X	X.X	X.X	X.X
		90% CI	XX - XX	XX - XX	XX - XX	XX - XX	XX - XX
	Ad Lib Use	n	X	X	X	X	X
		n missing	X	X	X	X	X
		Mean	X.X	X.X	X X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX
		Geom. Mean	X X	X.X	X.X	X.X	X.X
		Geom. CV%	X.X	X.X	X.X	X X	X.X
		90% CI	XX - XX	XX - XX	XX - XX	XX - XX	XX - XX

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

Programmer Note: All HPT parameters will be included in the summary table. Check the actual data for the decimal points of each parameter.

Table 15.2.6.1.1 will have the following format:

Table 15.2.6.1.1 Product-use-emergent Adverse Event Frequency by Product – Number of Subjects Reporting the Event (% of Subject Used Study Product) (Safety Population)

	Study Product						
Adverse Event*	**Day-2 P4M3-1.7%**	**Subject's Own e-Cigarette**	**P4M3-1.7%**	**P4M3-1.7%LA**	**P4M3-3%LA**	**P4M3-4%LA**	**Overall**
Number of Subjects Who Received Study Product	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (XXX%)
Number of Subjects With PUEAE	X (X%)	X (XX%)	X (X%)	X (X%)	X (XX%)	X (X%)	XX (XX%)
Number of Subjects Without PUEAE	XX (XX%)	X (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Eye disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vision blurred	X (X%)	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%)	X (X%)
Dyspepsia	X (X%)	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%)	X (X%)
Musculoskeletal and connective tissue disorders	X (X%)	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%)	X (X%)
Muscle cramps	X (X%)	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%)	X (X%)
Nervous system disorders	X (X%)	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%)	X (X%)
Reproductive system and breast disorders	X (X%)	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%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Epistaxis	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Skin and subcutaneous tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Sweating increased	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Note: *Adverse events are classified according to MedDRA Version 20.0
PUEAE = Product-use-emergent adverse event
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM

Table 15.2.6.1.2 will have the following format:

Table 15.2.6.1.2 Product-use-emergent Adverse Event Frequency by Product – Number of Adverse Events (% of Total Adverse Events) (Safety Population)

	Study Product						
Adverse Event*	**Day-2 P4M3-1.7%**	**Subject's Own e-Cigarette**	**P4M3-1.7%**	**P4M3-1.7%LA**	**P4M3-3%LA**	**P4M3-4%LA**	**Overall**
Number of PUEAEs	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (XXX%)
Eye disorders	X (X%)	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%)	X (X%)
Gastrointestinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	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%)	X (X%)
Back pain	X (X%)	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%)	X (X%)
Musculoskeletal pain	X (X%)	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%)	X (X%)
Headache NOS	X (X%)	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%)	X (X%)
Vaginal discharge	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Epistaxis	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Skin and subcutaneous tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Sweating increased	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Note: *Adverse events are classified according to MedDRA Version 20.0
PUEAE = Product-use-emergent adverse event
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progname.sas DDMMMYYYY HH:MM

Table 15.2.6.1.3 will have the following format:

Table 15.2.6.1.3 Product Use-Emergent Adverse Event Frequency by Product, Severity, and Relationship to Study Product - Number of Adverse Events (Safety Population)

Adverse Event*	Study Product	Number of Study Product Use-Emergent Adverse Events	Severity			Relationship		
			Mild	Moderate	Severe	Not Related	Related to Study Procedure	Related to Study Product
Abdominal pain	XXXXXXX	X	X	X	X	X	X	X
Constipation	XXXXXXX	X	X	X	X	X	X	X
Dry throat	XXXXXXX	X	X	X	X	X	X	X
Dysmenorrhoea	XXXXXXX	X	X	X	X	X	X	X
Dyspepsia	XXXXXXX	X	X	X	X	X	X	X
Headache	XXXXXXX	X	X	X	X	X	X	X
	XXXXXXX	X	X	X	X	X	X	X
Myalgia	XXXXXXX	X	X	X	X	X	X	X
Nasal congestion	XXXXXXX	X	X	X	X	X	X	X
Skin laceration	XXXXXXX	X	X	X	X	X	X	X
Day -2 P4M3-1.7%		X	X	X	X	X	X	X
Subject Own e-Cigarette		X	X	X	X	X	X	X
P4M3-1.7%		X	X	X	X	X	X	X
P4M3-1.7%LA		X	X	X	X	X	X	X
P4M3-3%LA		X	X	X	X	X	X	X
P4M3-4%LA		X	X	X	X	X	X	X
Overall		X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 20.0.
Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 15.2.6.2.1 will have the following format:

Table 15.2.6.2.1 Serious Adverse Events (Safety Population)

There were no serious adverse events recorded during the study.

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

Tables 15.2.6.4.1, 15.2.6.4.2, and 15.2.6.4.3 will have the following format:

Table 15.2.6.4.1 Out-of-Range Values and Recheck Results - Clinical chemistry (Safety Population)

Subject Number	Age#/ Sex	Study Period	Day	Hour	Date	Time	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)	Parameter5 <Range> (Unit)
X	XX/X	Screen	.	.	DDMMMYYYY	HH:MM:SS	XX HN			XX HN	
		1	X	XX.XX	DDMMMYYYY	HH:MM:SS		XX LYG1	XX LN		XX LYG2

Note: # Age is calculated from the date of informed consent. F = Female, M = Male
H = Above normal range, L = Below normal range
PI Interpretation: - = Not clinically significant, + = Clinically significant
CTCAE grade: G1 = Mild, G2 = Moderate
Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Notes: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early termination chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for Tables 15.2.6.4.2 and 15.2.6.4.3 will resemble 15.2.6.4.1.

Programmer Notes: Clinically significant lab values generally will be captured as AEs, some of which the PI may indicate in Listing 15.3.4.3.1.5 lab comments (as per GPG.03.0028 sections 2.9 and 2.10). Derive an additional CS flag for PI flag (+) based on positive comments (i.e. CS/Clinically Significant). Present this derived 4th column in all tables, and list only subjects/tests which are PI-determined clinically significant lab values in Table 15.2.6.4.4.

Table 15.2.6.4.4 will have the following format:

Table 15.2.6.4.4 Clinically Significant Values and Recheck Results (Safety Population)

Subject Number	Age#/ Sex	Study Period	Day	Hour	Date	Time	Department	Test	Result	Normal Range	Unit
X	XX/X	1	X	X.X	DDMMMYYYY	HH:MM:SS	XXXXXXXXXXXXXXX	XXXXXXXXXXX	XXX HYR+	X – X	mg/dL
			X	X.X	DDMMMYYYY	HH:MM:SS	XXXXXXXXXXXXXXX	XXXXXXXXXXX	XXX	X – X	mg/dL

Note: # Age is calculated from the date of informed consent. F = Female, M = Male
H = Above normal range
PI Interpretation: R = Recheck requested, + = Clinically significant
Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

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

If no event meet these criteria then include a statement as follows:
"There were no clinical laboratory results documented as clinically significant by the PI."

Tables 15.2.6.5.3 and 15.2.6.5.5 will resemble Table 15.2.6.5.1

Table 15.2.6.5.1 Clinical Laboratory Summary and Change from Baseline - Clinical chemistry (Safety Population)

			Original Value				Change From Baseline	
				Admission		Discharge		Discharge
Laboratory Test (units)	Normal Range	Statistic	Screen	Day -2	Day 2	Day 5	Day 2	Day 5
Testname (unit)	< - >#	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
Testname (unit)	< - >	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

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Listing 16.1.10.1 for the breakdown.
* Above Normal Range, ^ Below Normal Range
Baseline is the result closest and prior to the first product administration (Admission Day -2).
SD = Standard deviation
Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer note: Similar for remaining laboratory tests.

Tables 15.2.6.5.4 and 15.2.6.5.6 will resemble 15.2.6.5.2

Table 15.2.6.5.2 Clinical Laboratory Shift From Baseline - Clinical 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)	< - >	X	XX	X	X	XX	X	X	XX	X
	< - >	X	XX	X	X	XX	X	X	XX	X
	< - >	X	XX	X	X	XX	X	X	XX	X

Note: N = Within Normal Range, L = Below Normal Range, H = Above Normal Range
Baseline is the result closest and prior to the first product administration (Admission Day -2).
Program: /AAXXXXX/ECR/sas_prg/stsas/tab programe.sas DDMMMYYYY HH:MM

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

Table 15.2.6.5.7 will have the following format.

Table 15.2.6.5.7 Vital Sign Summary for Screening, Admission, and Discharge (Safety Population)

Vital Sign (units)	Statistic	Screen	Admission Day -2	Discharge Day 5
Testname (unit)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX
Testname (unit)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX

Note: SD = Standard deviation
Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer note: Similar for remaining vital sign measurements.

Table 15.2.6.5.8 will have the following format.

Table 15.2.6.5.8 Vital Sign Summary for Days -1 through 4 and Change From Pre Product Use (Safety Population)

Vital Sign (units)	Product	Product Use	Statistic	Pre-Use	Post-Use	Change From Pre-Use
Testname (unit)	Subject Own e-Cigarette	Fixed Puff	n	X	X	X
			Mean	X.X	X.X	X.X
			SD	X.XX	X.XX	X.XX
			Minimum	XX	XX	XX
			Median	X.X	X.X	X.X
			Maximum	XX	XX	XX
		Ad Libitum	n	X	X	X
			Mean	X.X	X.X	X.X
			SD	X.XX	X.XX	X.XX
			Minimum	XX	XX	XX
			Median	X.X	X.X	X.X
			Maximum	XX	XX	XX

Note: SD = Standard deviation
Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer note: Similar for remaining products and vital sign measurements.

Table 15.2.6.5.9 will have the following format.

Table 15.2.6.5.9 12-Lead Electrocardiogram Summary and Change from Baseline (Safety Population)

		Original Value		Change From Baseline
Parameter (unit)	Statistic	Screen	Discharge Day 5	Discharge Day 5
Testname (unit)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX
Testname (unit)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX

Note: Baseline is the result closest and prior to the first product administration (Screen).
SD = Standard deviation
Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer note: Similar for remaining ECG parameters.

Table 15.2.6.5.10 will have the following format.

Table 15.2.6.5.10 12-Lead Electrocardiogram Shift From Baseline (Safety Population)

Baseline N			Baseline ANCS			Baseline ACS		
Post Product Use			Post Product Use			Post Product Use		
N	ANCS	ACS	N	ANCS	ACS	N	ANCS	ACS
X	X	X	X	X	X	X	X	X

Note: Baseline is the result closest and prior to the first product administration (Screen).
N = Normal, ANCS = Abnormal, Not Clinically Significant, ACS = Abnormal, Clinically Significant
Program: /CAXXXXX/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 15.2.6.5.11 will have the following format.

Table 15.2.6.5.11 Spirometry Summary (Safety Population)

		Screen		
Parameter (unit)	**Statistic**	**Pre-Bronchodilator**	**Post-Bronchodilator**	**Day 5 Post-Bronchodilator**
Testname (unit)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX
Testname (unit)	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Median	X.X	X.X	X.X
	Maximum	XX	XX	XX

Note: SD = Standard deviation
Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer note: Similar for remaining Spirometry parameters.

Table 15.2.6.5.12 will have the following format:

Table 15.2.6.5.12 Cough Assessment Summary (Safety Population)

			Subject Own e-Cigarette		--- P4M3-1.7%		P4M3-1.7%LA		P4M3-3%LA		P4M3-4%LA	
		Day -2	---	---	---	---	---	---	---	---	---	---
Question	Answer	P4M3-1.7%	Fixed	Ad lib	Fixed	Ad lib	Fixed	Ad lib	Fixed	Ad lib	Fixed	Ad lib
Need to Cough?	Yes	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	No	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Intensity*	1	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	2	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	3	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	4	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	5	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Frequency*	1	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	2	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	3	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	4	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	5	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
Amount of Sputum*	0	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	1	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	2	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	3	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)

Note: *Intensity: 1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe
*Frequency: 1 = rarely; 2 = sometimes; 3 = fairly often; 4 = often; 5 = almost always.
*Amount of sputum: 0 = no sputum; 1 = a moderate amount of sputum; 2 = a larger amount of sputum; 3 = a very large amount of sputum
Program: /CAXXXXX/sas_prg/stsas/tab cdash_demsum.sas DDMMMYYYY HH:MM

Table 15.2.6.5.13 will have the following format:

Table 15.2.6.5.13 Concomitant Medication Summary – Number of Subjects Used Concomitant Medication (% of Subject Used Study Product) (Safety Population)

Concomitant Medication*	Day-2 P4M3-1.7%	Sequence 1	Sequence 2
Number of Subjects Who Received Study Product	XX (100%)	XX (100%)	XX (100%)
Number of Subjects Used Concomitant Medication	X (X%)	X (XX%)	X (X%)
XXXXXXXXX	X (X%)	X (X%)	X (X%)
XXXXXXXXXXXX	X (X%)	X (X%)	X (X%)

Note: * Concomitant medication are classified according to WHO DD Version 01MAR2017.
Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM

17. 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 from the Celerion Celerion SDTM Version 1.4 data structure.

Listing 15.3.1.1.1 Inclusion Criteria

X. <>
X. <>
X. <>
X. <>
X. <>
X. <>
X. <>
X. <>
X. <>

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

Listing 15.3.1.1.2 Inclusion Criteria Responses (Safety Population)

Subject Number	Study Period	Inclusion Criteria									
		1	2	3	4	5	6	7	8	9	10
X	Screening	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX

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

Listing 15.3.1.2.1 Exclusion Criteria

X. <>
X.
X.
X.
X.
X.
X.
X.
X.
XX.
XX.
XX.
XX.
XX.
XX.

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

Listing 15.3.1.2.2.1 Exclusion Criteria Responses (I of II) (Safety Population)

Subject Number	Study Period	Exclusion Criteria										
		1	2	3	4	5	6	7	8	9	10	11
X	Screening	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX

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

Listing 15.3.1.2.2.2 Exclusion Criteria Responses (II of II) (Safety Population)

Subject Number	Study Period	Exclusion Criteria										
		12	13	14	15	16	17	18	19	20	21	22
X	Screening	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX

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

Listing 15.3.1.3 Subject Eligibility at Check-in (Safety Population)

Subject Number	Study Period	Visit Date	Did the Subject Still Meet all Eligibility Criteria at the Time of Admission ?	If no, Then Comment Which Criteria Were Violated?	Comment
X	Admission	DDMMMYYYY	XXX		

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

Listing 15.3.1.4 Demographics (Safety Population)

Subject Number	Visit Date	Age (yrs)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)	Informed Consent Date	Informed Consent Time
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX	DDMMMYYYY	HH:MM
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX	DDMMMYYYY	HH:MM
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX	DDMMMYYYY	HH:MM
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX	DDMMMYYYY	HH:MM
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX	DDMMMYYYY	HH:MM
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX	DDMMMYYYY	HH:MM
X	DDMMMYYYY	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX	DDMMMYYYY	HH:MM

Note: Age is calculated based on the ICF date and birth date.
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.1.5.1 Physical Examination (I of II) (Safety Population)

Subject Number	Study Period	Day	Date	Was PE Performed?	System1	System2	System3	System4	System5	System6
X	Screening	.	DDMMMYYYY	XXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX
	Admission	-2	DDMMMYYYY	XXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX
	Discharge	5	DDMMMYYYY	XXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX

Note: See Listing 15.3.1.5.3 for physical examination Abnormality descriptions.
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.1.5.2 Physical Examination (II of II) (Safety Population)

Subject Number	Study Period	Day	Date	System7	System8	System9	System10	System11	etc.
X	Screening	.	DDMMMYYYY	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX
	Admission	-2	DDMMMYYYY	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX
	Discharge	5	DDMMMYYYY	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX	XXXXXXX

Note: See Listing 15.3.1.5..3 for physical examination abnormality descriptions.
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.1.5.3 Physical Examination Descriptions (Safety Population)

Subject Number	Study Period	Day	Date	Result	System	Description or Comment	NCS	CS
X	Screening	.	DDMMMYYYY	ABNORMAL	Skin	RIGHT CHEST SCAR	X	
X	Screening	.	DDMMMYYYY	ABNORMAL	Skin	RIGHT CHEST SCAR	X	

Note: NCS = Not clinically significant, CS = Clinically significant
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.1.6 Medical and Surgical History (Safety Population)

Subject Number	Any History?	Study Period	Seq#	Description	Date of Diagnosis/Surgery		Ongoing?
					Start	End	
X	XXX	Screening	X	XXXXX	MM/YYYY	MM/YYYY	XXX

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

Listing 15.3.1.7 Smoking History and e-Cigarette Use (Safety Population)

Subject Number	Study Period	Visit Date	Visit Time	Question	Answer
X	Screening	DDMMMYYYY	HH:MM	1. Have you ever smoked 100 cigarettes or more in your life?	XXX
				2. XXXXXXXXXXXXXXXXXXXXXXXXXX	XXX

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

Listing 15.3.1.8 Subject Discontinuation (Safety Population)

Subject Number	Product Sequence	Date of Last Visit	Completed Study?	Reason for Discontinuation	Comment
X	X	DDMMMYYYY	Yes		
X	X	DDMMMYYYY	Yes		
X	X	DDMMMYYYY	Yes		
X	X	DDMMMYYYY	Yes		
X	X	DDMMMYYYY	No	Personal Reason	
X	X	DDMMMYYYY	Yes		
X	X	DDMMMYYYY	Yes		
X	X	DDMMMYYYY	Yes		

Note: Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.2.1 Randomization (Safety Population)

Subject Number	Study Period	Visit Date	Time	Randomization Sequence
X	Day 1	DDMMMYYYY	HH:MM	1 - P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA

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

Listing 15.3.2.2.1 Fixed Puffing Product Use With HPT (I of II) (Safety Population)

Subject Number	Study Day	Study Product	Date	Start Time	Stop Time	Cartridge Weight (mg)			Comment
						Pre-Use	Post-Use	Difference	
X	-1	Subject's Own e-cigarette	DDMMMYYYY	HH:MM	HH:MM	XXXX.X	XXXX.X	XXXX.X	XXXXXX

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

Listing 15.3.2.2.2 Fixed Puffing Product Use With HPT (II of II) (Safety Population)

Subject Number	Study Day	Study Product	Date	Total Puff Volume (mL)	Average Puff Volume (mL)	Average Flow (mL/sec)	Average Puff Duration (sec)	Comment
X	-1	Subject's Own e-cigarette	DDMMMYYYY	XXXXX.XXX	XXXX.XXX	XXX.XXX	XX.XXX	

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

Listing 15.3.2.3.1 Ad lib Product Use With HPT (I of II) (Safety Population)

Subject Number	Study Day	Study Product	Date	Start Time	Stop Time	Cartridge Weight (g)			Total Puffs per 60 min
						Pre-Use	Post-Use	Difference	
X	-1	Subject's Own e-cigarette	DDMMMYYYY	HH:MM	HH:MM	X.XXXX	X.XXXX	X.XXXX	XXX

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

Listing 15.3.2.3.2 Ad Lib Product Use With HPT (II of II) (Safety Population)

Subject Number	Study Day	Study Product	Date	Total Puff Volume (mL)	Average Puff Volume (mL)	Average Flow (mL/sec)	Average Puff Duration (sec)	Comment
X	-1	Subject's Own e-cigarette	DDMMMYYYY	XXXXX.XXX	XXXX.XXX	XXX.XXX	XX.XXX	

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

Listing 15.3.3.1 VAS Craving Assessment (Pharmacodynamic Population)

Subject Number	Study Day	Study Product	Product Use	Time Point	Was VAS Assessment Performed?	Date	Time	How strong is your craving for using an electronic cigarette?	Comment
X	X	XXXXXXX	Fixed Puffing	Pre-Product Use	XXX	DDMMMYYYY	HH:MM	XX	
				4-Minutes Post Product Use	XXX	DDMMMYYYY	HH:MM	XXX	

Note: 1 = Not craving, 5 = strong craving
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.3.2 Sensory Questionnaire (Pharmacodynamic Population)

Subject Number	Study Day	Study Product	Product Use	Was Sensory Questionnaire Performed?	Date	Time	Sensory Questions 1	2	3	4	5	6	7	8	Comment
X	X	XXXXX	Fixed Puffing	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	
			Ad Lib Use	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	
	X	XXXXXX	Fixed Puffing	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	
			Ad Lib Use	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	
	X	XXXXXXX	Fixed Puffing	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	
			Ad Lib Use	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	

Note: 1. How much did you like the puffs you took? 2. How harsh were the puffs you took?
3. How similar to your own brand were the puffs? 4. Strength of puffs on tongue?
5. Strength of puffs in nose? 6. Strength of puffs in back of mouth & throat?
7. Strength of puffs in windpipe? 8. Strength of puffs in chest?
1 = Not at all, 2 = Very little, 3 = Little, 4 = Moderately, 5 = A lot, 6 = Quite a lot, 7 = Extremely
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.3.3.1 Adapted mCEQ Questionnaire (Original Score) (Pharmacodynamic Population)

Subject Number	Study Day	Study Product	Was Adapted mCEQ performed?	Date	Time	mCEQV 1	2	3	4	5	6	7	8	9	10	11	12
X	X	XXXX X	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	X	X	X	X
	X	XXXXXXX	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	X	X	X	X
	X	XXXXXX	XXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	X	X	X	X

Note: 1. Was it satisfying? 2. Did it taste good?
3. Did you enjoy the sensations in your throat and chest? 4. Did it calm you down?
5. Did it make you feel more awake? 6. Did it make you feel less irritable?
7. Did it help you concentrate? 8. Did it reduce your hunger for food?
9. Did it make you dizzy? 10. Did it make you nauseated?
11. Did it immediately relieve your craving for an electronic cigarette? 12. Did you enjoy it?
1 = Not at all, 2 = Very little, 3 = Little, 4 = Moderately, 5 = A lot, 6 = Quite a lot, 7 = Extremely
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.3.3.2 Adapted mCEQ Questionnaire (Subscale Score) (Pharmacodynamic Population)

Subject Number	Study Day	Study Product	Date	Time	Satisfaction	Psychological Reward	Aversion	Enjoyment of Sensation	Craving Reduction
X	X	XXXXX	DDMMMYYYY	HH:MM:SS	X	X	X	X	X
	X	XXXXX	DDMMMYYYY	HH:MM:SS	X	X	X	X	X
	X	XXXXX	DDMMMYYYY	HH:MM:SS	X	X	X	X	X

Note: 1. Was it satisfying? 2. Did it taste good?
3. Did you enjoy the sensations in your throat and chest? 4. Did it calm you down?
5. Did it make you feel more awake? 6. Did it make you feel less irritable?
7. Did it help you concentrate? 8. Did it reduce your hunger for food?
9. Did it make you dizzy? 10. Did it make you nauseated?
11. Did it immediately relieve your craving for an electronic cigarette? 12. Did you enjoy it?
Satisfaction: average of 1, 2, 12;
Psychological reward: average of 4 to 8;
Aversion: average of 9, 10;
Enjoyment of sensation: 3;
Craving Reduction: 11
1 = Not at all, 2 = Very little, 3 = Little, 4 = Moderately, 5 = A lot, 6 = Quite a lot, 7 = Extremely
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.4.1.1 Blood Draw Times (Safety Population)

Subject Number	Study Product	Study Day	Product Use	Time	Collection Date	Actual Time	Comments
X	XXXXXX	X	Fixed Puffing	Pre Product Use	DDMMMYYYY	HH:MM:SS	
				X Minutes Post Product Use	DDMMMYYYY	HH:MM:SS	
				X Minutes Post Product Use	DDMMMYYYY	HH:MM:SS	
				X Minutes Post Product Use	DDMMMYYYY	HH:MM:SS	

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

Listing 15.3.4.1.2 Meal Times (Safety Population)

Subject Number	Study Day	Visit Date	Was Subject Compliant With Dietary Requirements?	Meal Event	Not Done?	Start Time	Stop Time	Comments
X	X	DDMMMYYYY	XXXX	XXXXXXX		HH:MM	HH:MM	

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

Listing 15.3.4.1.3 Prior and Concomitant Medications (Safety Population)

Subject Number	Study Product	Any Med?	Medication (WHO DD* Term)	Dosage	Route	Start Date	Start Time	Stop Date	Stop Time	Freq.	Indication	Continuing?	MH #	Due to AE?
X	XXXXX	None	XXXXXXXXX (XXXXXXXXXX)	620 mg	ORAL	DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	Once	Toothache	No		XXX

Note: * Concomitant medications are coded with WHO Drug Dictionary Version 01MAR2017.
Freq. = Frequency
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.4.1.4 Concomitant Procedures (Safety Population)

Subject Number	Study Product	Any Procedure?	Procedure	Start Date	Start Time	Stop Date	Stop Time	Procedure Ongoing at End-of-Study?	Reason for Procedure
X	XXXXXX	XXX	XXXXXXX	DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	XXX	XXXXXX

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

Listing 15.3.4.2.1.1 Adverse Events (I of II) (Safety Population)

Subject Number	Study Product	UE?^	Adverse Event*	Preferred Term	Time from Last Product (DD:HH:MM)	Start Date	Start Time	Stop Date	Stop Time	Duration (DD:HH:MM)
1	XXXX	Yes	XXXXXXXXXXXXX	XXXXXXXXXX XX	XX:XX:XX	DDMMMYYYY	X:XX	DDMMMYYYY	X:XX	XX:XX:XX

Note: ^ = Abbreviation for study product use-emergent (UE),
* = Adverse events are coded according to the MedDRA Version 20.0.
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.4.2.1.2 Adverse Events (II of II) (Safety Population)

Subject Number	Study Product	Adverse Event	Onset Date	Onset Time	Freq	Severity	Ser*	Outcome	Relation-ship to Study product	Action	Other Action	Cause Study Discontinuation?
1	XXXXXX	None XXXXXXXXXX	DDMMMYYYY	X:XX	Inter.	Mild	NS	Resolved	XXXXXXXX	None		XX

Note: Ser* represents Serious: NS = Not Serious
Freq represents Frequency: SI = Single Episode, Inter. = Intermittent, Cont. = Continuous
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.4.2.2.1 Adverse Device Events (I of II) (Safety Population)

Subject Number	Study Product	Any Event	Event Related to	Unique Device ID	Adverse Device Event Term	Onset		Resolved		Duration
						Date	Time	Date	Time	(DD:HH:MM)
1	XXXX	XXX	XXXXXXX	XXX	XXXXXXXXXX XX	DDMMMYYYY	X:XX	DDMMMYYYY	X:XX	XX:XX:XX

Note: ^ = Abbreviation for study product use-emergent (UE),
* = Adverse events are classified according to the MedDRA Version 20.0.
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.4.2.2.2 Adverse Device Events (II of II) (Safety Population)

Subject Number	Study Product	Adverse Device Event Term	Onset		Severity	Relation-ship to Adverse Event	Adverse Event	Action Taken with the Device
			Date	Time				
X	XXXXXX	XXXXXXXXXX	DDMMMYYYY	X:XX .	Minor	XXXXXXXX	XXXXX	XX

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

Listing 15.3.4.2.3 Adverse Event Preferred Term Classification (Safety Population)

Subject Number	Study Product	Adverse Event	Preferred Term	Body System	Onset Date	Onset Time
X	XXXX	XXXXXXX	XXXXXX XXXXXXXXX	XXXXXXX XXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	X:XX

Note: * = Adverse events are classified according to the MedDRA Version 20.0.
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendices 15.3.4.3.1.2 to 15.3.4.3.1.4 will have the following format.

Listing 15.3.4.3.1.1 Clinical Chemistry (Safety Population)

Subject Number	Age#/ Sex	Study Day	Hour	Date	Time	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)	Parameter5 <Range> (Unit)
X	XX/X	Screen	.	DDMMMYYYY	HH:MM:SS	XX HNG1	XXX	XXX	XXX	XX HN
		X	XX.XX	DDMMMYYYY	HH:MM:SS	XX	XX	XXX	XXX	XX

Note: # Age is calculated from the date of informed consent. F = Female, M = Male
H = Above normal range, L = Below normal range
PI Interpretation: N = Not clinically significant, Y = Clinically significant
CTCAE Grade: G1 = Mild
Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study. Please add study day column when appropriate (i.e. in the UDS listing).

Listing 15.3.4.3.1.5 Clinical Laboratory Report – Comments (Safety Population)

Subject Number	Study Day	Date	Lab Panel	Test	Result	Unit	Comment
X	X	DDMMMYYYY	XXXXXXX	XXXXXXXXX	XXX	XXX	XXXXXX

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

Listing 15.3.4.3.1.6 Breath Alcohol Screen (Safety Population)

Subject Number	Study Day	Visit Date	Was Breath Alcohol Test Done?	Actual Time	Result	Comment
X	Screening Day X	DDMMMYYYY DDMMMYYYY	XXX XXX	HH:MM HH:MM	Negative Negative	

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

Listing 15.3.4.3.1.7 Carbon Monoxide Breath Test (Safety Population)

Subject Number	Study Day	Visit Date	Was Carbon Monoxide Breath Test Done?	Actual Time	Result (ppm)	Comment
X	Screening	DDMMMYYYY	XXX	HH:MM	XX	
	Day X	DDMMMYYYY	XXX	HH:MM	XX	

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

Listing 15.3.4.3.1.8 Urine Drug Screen (Safety Population)

Subject Number	Study Day	Visit Date	Was Urine Drug Screen Done?	Actual Time	Result	If Positive, list all that were positive	Comment
X	Screening	DDMMMYYYY	XXX	HH:MM	Negative		
	Day -2	DDMMMYYYY	XXX	HH:MM	Negative		

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

Listing 15.3.4.3.1.9 Urine Cotinine (Safety Population)

Subject Number	Study Day	Visit Date	Was Urine Cotinine Done?	Actual Time	Result	Comment
X	Screening	DDMMMYYYY	XXX	HH:MM	Positive (>200 ng/mL)	
	Day -2	DDMMMYYYY	XXX	HH:MM	Positive (>200 ng/mL)	

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

Listing 15.3.4.3.1.10 Urine Pregnancy Test (Safety Population)

Subject Number	Study Day	Visit Date	Was Urine Pregnancy Test Done?	Reason for Not Done	Actual Time	Result	Comment
X	Day -2	DDMMMYYYY	XXX		HH:MM	Negative	
	Discharge	DDMMMYYYY	XXX		HH:MM	Negative	

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

Listing 15.3.4.3.2 Vital Signs (Safety Population)

Subject Number	Study Day	Study Product	Product Use	Visit Date	Time point	Blood Pressure (mmHg) Time	Test	Systolic/Diastolic	Pulse Rate (bpm)	Respiration Rate (rpm)
X	Screening			DDMMMYYYY		HH:MM	SUP5	XXX/XX	XX	XX
	Day -2			DDMMMYYYY		HH:MM	SUP5	XXX/XX	XX	XX
	Day -1	XXXXX	Fixed Puffing	DDMMMYYYY	Pre-Product Use	HH:MM	SUP5	XXX/XX	XX	XX
					60 Minutes Post Use	HH:MM	SUP5	XXX/XX	XX	XX
			Ad Lib use	DDMMMYYYY	Pre-Product Use	HH:MM	SUP5	XXX/XX	XX	XX
					60 Minutes Post Use	HH:MM	SUP5	XXX/XX	XX	XX
	Day 1	XXXXX	Fixed Puffing	DDMMMYYYY	Pre-Product Use	HH:MM	SUP5	XXX/XX	XX	XX
					60 Minutes Post Use	HH:MM	SUP5	XXX/XX	XX	XX
			Ad Lib use	DDMMMYYYY	Pre-Product Use	HH:MM	SUP5	XXX/XX	XX	XX
					60 Minutes Post Use	HH:MM	SUP5	XXX/XX	XX	XX

Note: SUPX = X-minute supine
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.4.3.3 12-Lead Electrocardiogram (Safety Population)

Subject Number	Study Day	Visit Date	Time	Result	Heart Rate (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTcB* (msec)	QTcF* (msec)	Comments
X	Screening	DDMMMYYYY	HH:MM	Normal	XX	XXX.X	XX.X	XXX.X	XXX.X	XXX.X	
	Discharge	DDMMMYYYY	HH:MM	Abnormal, NCS	XX	XXX.X	XX.X	XXX.X	XXX.X	XXX.X	XXXXXXXXXX

Note: QTcB* = QTc corrected using Bazett's correction, QTcF* = QTc corrected using Fridericia's correction.
NCS = Not clinically significant
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 15.3.4.3.4 Pulmonary Function Test (Safety Population)

Subject Number	Study Day	Visit Date	Time Point	Was the PFT Performed?	Time	FEV1 (L)	FEV1 %Predicted (L)	FVC (L)	FEV1/FVC (%)	Comments
X	Screening	DDMMMYYYY	Pre-Bronchodilator	YES	HH:MM	XX	XX	XX	XX	
			Post-Bronchodilator	YES	HH:MM	XX	XX	XX	XX	
	Discharge	DDMMMYYYY	Post-Bronchodilator	YES	HH:MM	XX	XX	XX	XX	

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

Programmer Note: Check actual data for the decimal points of each parameter.

Listing 15.3.4.3.5 Cough Assessment (Safety Population)

Subject Number	Study Day	Study Product	Visit Date	Product Use	Was Cough Assessment Performed?	Time	Need to Cough?	Cough Assessment Question 1	2	3	4	Any other Important Observations?
X	Day -2		DDMMMYYYY		YES	HH:MM	XX	XX	XX	XX	XX	XXXXXXXXXX
	Day -1	XXXXXX	DDMMMYYYY	Fixed Puffing	YES	HH:MM	XX	XX	XX	XX	XX	
				Ad lib Use	YES	HH:MM	XX	XX	XX	XX	XX	
	Day 1	XXXXXX	DDMMMYYYY	Fixed Puffing	YES	HH:MM	XX	XX	XX	XX	XX	
				Ad lib Use	YES	HH:MM	XX	XX	XX	XX	XX	
	Day 2	XXXXXX	DDMMMYYYY	Fixed Puffing	YES	HH:MM	XX	XX	XX	XX	XX	
				Ad lib Use	YES	HH:MM	XX	XX	XX	XX	XX	

Note: 1: Cough Impact Scale - How much is your cough bothering you? (1 = Not Bothering at all to 5 = Extremely bothersome).
2: Cough Intensity Scale - How intense is your cough? (1 = Very Mild, 2 = Mild, 3 = Moderate, 4 = Severe, 5 = Very severe).
3: Cough Frequency Scale - How frequently do you normally have to cough each day? (1 = Rarely, 2 = Sometimes, 3 = Fairly often, 4 = often, 5 = Almost always).
4: Sputum Production - To what extent do you produce sputum when coughing? (1 = No sputum, 2 = a Moderate amount of sputum, 3 = A large amount of sputum, 4 = A very large amount of sputum).
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Listing 16.1.9.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Normal Range	Unit
Clinical chemistry	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
Hematology	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units

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

Programmer Note: Similar for remaining Laboratory Groups and Test Names.