PMI RESEARCH & DEVELOPMENT

STATISTICAL ANAYSIS PLAN

A single-center, randomized, controlled, open-label, cross-over study in healthy subjects to investigate the nicotine pharmacokinetic profiles of 2 variants of P4M3 Gen 2.0, an electronic nicotine delivery system, compared to cigarettes

Protocol No: P4-PK-04-US

Final Protocol Version 1.0 Date: 28 September 2021
Final Protocol Version 2.0 Date: 14 October 2021

Product Name: P4M3 Gen 2.0

Final Version 1.0
Date: 21 March 2022

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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Issue Date: 21 March 2022

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Signature: DocuSigned by:
Signing Reason: I approve this document
Signing Time: 21-Mar-2022 | 22:25:15 GMT
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Date: _____

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Principal Scientist

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Signing Reason: I approve this document
Signing Time: 21-Mar-2022 | 22:09:21 GMT
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TABLE OF CONTENTS

1. INTRODUCTION

This SAP has been developed to supplement the statistical analyses described in the clinical study protocol final version 2.0 dated 14 October 2021.

This SAP describes the methodology and considerations of the planned analyses and a list of all the TFLs for this study. Any changes to the TFL shells numbering or to the title of the TFLs will not require an amendment to this SAP.

This SAP and any amendments will be finalized prior to the lock of the clinical database. Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses, will be described in the clinical study report (CSR).

The preparation of this SAP is based on the following documents:

- International Council on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials".
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports".
- Case report form (CRF) final version 4.0 dated 07 March 2022.
- Clinical Study Protocol (CSP) final version 2.0 dated 14 October 2021.

1.1 Revision History

Version	Date of Revision	Revision
Final version 1.0	21 Mar 2022	Original Version

Any additional exploratory 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 CSR.

2. OBJECTIVES AND ENDPOINTS

Main Objective and Endpoints:

The main objective of this study is:

1. To describe the plasma concentration-time profile of nicotine and derived pharmacokinetic (PK) parameters of 2 variants of P4M3 Gen 2.0 and cigarettes from 6 minutes *ad libitum* use.

   Related Endpoints (Day 1 to Day 3):

   - Background-corrected maximum plasma concentration [C_{max}]
   - Background-corrected time to the maximum concentration [T_{max}]
   - Area under the background-corrected concentration-time curve (AUC) from start of product use (T_0) to 2 minutes, to 4 minutes, to T_{max}, to 10 hours, to time of last quantifiable concentration and extrapolated to infinity [$AUC_{0\text{-}2min}$, $AUC_{0\text{-}4min}$, $AUC_{0\text{-}Tmax}$, $AUC_{0\text{-}10h}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}infinity}$]

     Maximum ratio of background-corrected concentration over time, from T_0 (excluded) to T_{max} (included) [$_{max}(C_t/t)_{t\in]0,Tmax]}$]

Secondary Objective and Endpoints:

The secondary objectives of this study are:

1. To describe pharmacodynamic (PD) effects (subjective effects and related behavioral assessments) of 2 variants of P4M3 Gen 2.0 and cigarettes from 6 minutes *ad libitum* use.

   Related Endpoints (Day 1 to Day 3):

   - Score from cigarette craving by the visual analog sale (VAS)-craving assessment
   - Score from product evaluation by Assessment of Behavioral Outcomes related to Tobacco and nicotine products (ABOUT)-Product experience questionnaire
   - Score from product liking by the VAS-liking assessment

2. To describe human puffing topography (HPT) of 2 variants of P4M3 Gen 2.0 from the 6 minutes *ad libitum* use.

   Related Endpoints (Day 1 to Day 3):

   - Per-puff parameters and per-product use experience parameters from the MDEDR puffing topography device for 2 variants of P4M3 Gen 2.0

3. To describe the extent of product use from 2 variants of P4M3 Gen 2.0 from the 6 minutes *ad libitum* use.

   Related Endpoints (Day 1 to Day 3):

   - Amount of nicotine delivered derived from the weighing of P4M3 Gen 2.0 Cartridge before and after use

4. To evaluate the safety and tolerability during the study.

   Related Endpoints (From Enrollment to End-of-Study [EOS]):

   - Incidence of adverse events (AEs) and serious adverse events (SAEs)
   - Incidence of P4M3 Gen 2.0 product events including malfunction/misuse
   - Changes in physical examination from baseline
   - Changes in electrocardiogram (ECG) from baseline (heart rate, PR, QRS, QT, QTcF interval)
   - Changes in vital signs from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
   - Concomitant medication
   - Changes in standard spirometry from baseline (FEV1, FEV1% predicted, FVC, FVC% predicted, FEV1/FVC)
   - Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel

Exploratory Objectives and Endpoints:

1. To describe the associations between P4M3 Gen 2.0 HPT parameters, PD and PK parameters.

   Related Endpoints (Day 1 to Day 3):

   - Score from product liking by the VAS-liking assessment and C_{max}, T_{max}, and $AUC_{0\text{-}infinity}$ PK endpoints
   - Score from product liking by the VAS-liking assessment and per-product use experience parameters from the MDEDR puffing topography device for 2 variants of P4M3 Gen 2.0

Additional Study Assessments (for eligibility assessment and baseline characteristics):

- Serology for human immunodeficiency virus (HIV) 1/2 and hepatitis B and C
- Pregnancy test (all females)
- Urine cotinine test
- Urine drug test including testing for amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates
- Alcohol breath test
- Nicotine dependence assessed by Fagerström Test for Nicotine Dependence
- Cytochrome P450 2A6 (CYP2A6) activity expressed as trans-3'-hydroxycotinine / cotinine molar metabolite ratio in plasma

Study Hypothesis:

This study is exploratory in nature and there is no pre-specified hypothesis to be tested.

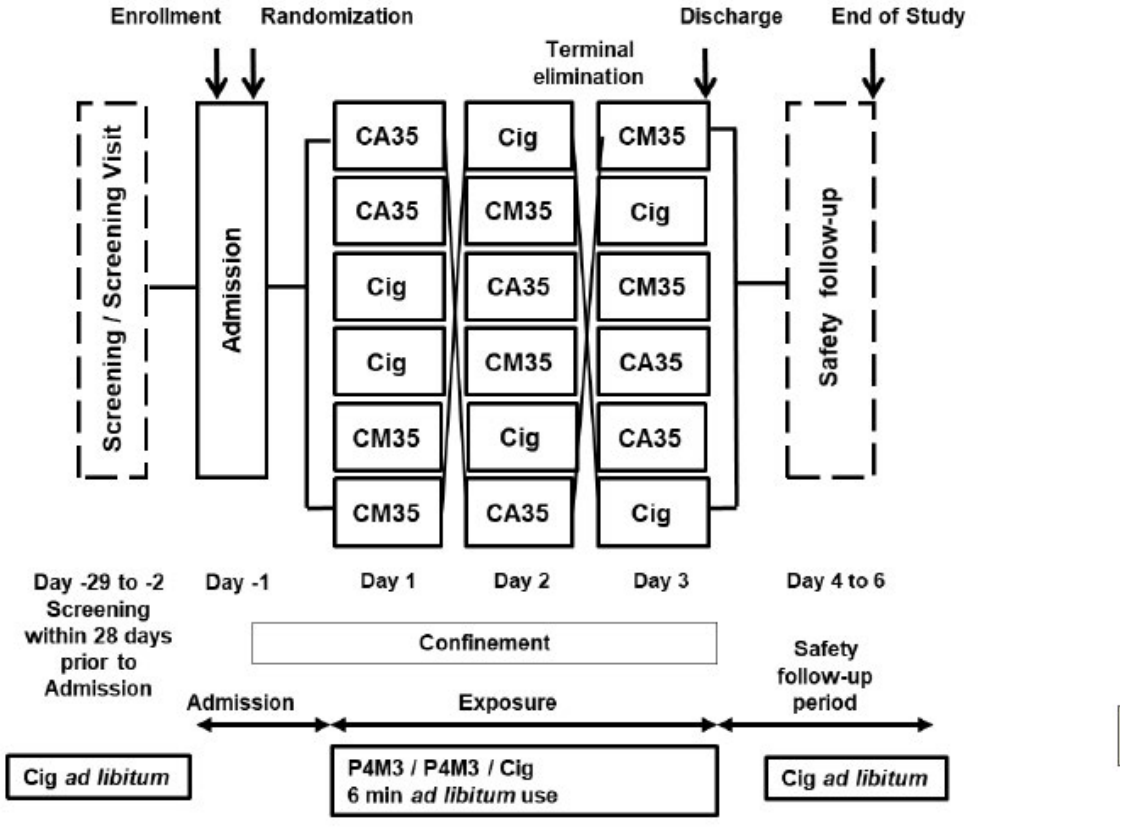
3. INVESTIGATION PLAN

3.1 STUDY DESIGN

This is a single-center, randomized, controlled, open-label, crossover study to investigate the nicotine PK profiles of variants of P4M3 Gen 2.0, an electronic nicotine delivery system (ENDS), compared to cigarettes. In addition, PD effects (subjective effects and related behavioral assessments) will be evaluated to provide further insights on product evaluation. The study will be conducted with 3 periods and 6 sequences in a cross-over design.

A Screening Visit will be conducted within 28 days (Day -29 to Day -2) prior to Admission (Day -1) to the investigational site (Figure 1). The investigational site staff will do a demonstration of P4M3 Gen 2.0, without product use, during the Screening Visit.

Figure 1 Study Design



Abbreviations: CM35 = P4M3 Gen 2.0 Classic Menthol 3.5% nicotine; CA35 = P4M3 Gen 2.0 Classic Auburn 3.5% nicotine; Cig= Subjects' own cigarette smoking; P4M3 = Electronic Nicotine Delivery System P4M3 Gen 2.0

Qualified subjects will return to the investigational site for Day -1. Subjects should have fasted for at least 10 hours prior to the safety laboratory assessments. After confirmation of eligibility, subjects will be enrolled. All subjects that are not enrolled will be considered as screen failures.

On Day -1, enrolled subjects will perform a product test using P4M3 Gen 2.0 Classic Auburn 3.5% (CA35) variant *ad libitum* for up to 10 minutes. After the product test, subjects not willing and/or not ready to use P4M3 Gen 2.0 during the study will be discontinued from the study, will enter the 3-day Safety Follow-up and will be replaced.

Subjects willing and ready to use 2 variants of P4M3 Gen 2.0 during the study after product test will start their confinement period of 3 days. The brand of subjects' cigarettes will be recorded.

Thirty-six (36) subjects will be randomized to 1 of 6 possible sequences of product use on Day 1 to Day 3 (see Figure 1). On Day 1 to Day 3, after at least 12 hours of abstinence from any nicotine/tobacco containing products (nicotine wash-out), subjects will smoke a cigarette or use a variant of P4M3 according to randomized product use sequence *ad libitum* for 6 minutes (± 30 seconds). The weight of each P4M3 Gen 2.0 Cartridge will be determined before and after product use to estimate the amount of nicotine delivered in the aerosol during the 6-minute *ad libitum* use period. Subjects will use a variant of P4M3 Gen 2.0 with the MDEDR puffing topography device connected with data recording *ad libitum* for 6 minutes (± 30 seconds).

Subjects will complete questionnaires about product evaluation, craving and liking assessments.

The start of product use of the 6 minutes *ad libitum* use period will be defined as T_0. T_0 on Day 1 to Day 3 should be at approximately the same time in the morning, within a window of ± 20 minutes. Venous blood samples will be obtained according to the standard operating procedures (SOPs) at the investigational site.

On Day 1, 15 blood samples will be collected for determination of nicotine concentration at the following time points in relation to T_0 with a time window as indicated in brackets:

Prior to T_0:

- T-1: 5 minutes (± 1 minute)

After T_0:

- T1 after 1 minute (+ 30 seconds)
- T2 after 2 minutes (+ 1 minute)
- T3 after 4 minutes (+ 1 minute)
- T4 after 6 minutes (+ 1 minute)
- T5 after 8 minutes (+ 1 minute)
- T6 after 10 minutes (+ 1 minute)
- T7 after 12 minutes (+ 1 minute)
- T8 after 15 minutes (± 2 minutes)
- T9 after 30 minutes (± 2 minutes)
- T10 after 1 hour (± 5 minutes)
- T11 after 2 hours (± 5 minutes)
- T12 after 4 hours (± 5 minutes)

- T13 after 10 hours (± 5 minutes)
- T14 after 24 hours (± 10 minutes) (Day 1 and Day 2 only)

On Day 2, 14 blood samples will be collected for determination of nicotine PK after allocated product use at the same time points, except time point T-1. The sample T14 after T0 on Day 1 will also be used to determine the nicotine baseline concentration prior to T0 on Day 2 and similarly, T14 after T0 on Day 2 for nicotine baseline concentration prior to T0 on Day 3.

On Day 3, 13 blood samples will be collected for determination of nicotine PK after allocated product use. The sample T14 after T0 on Day 3 will not be collected.

On Day 1 to Day 3, subjective effects of liking and craving will be assessed using a VAS (100 mm going from "strong disliking" to "strong liking" for VAS liking, and from "no craving" to "strong craving" for VAS craving) at the following time points in relation to T_0:

Prior to T_0 (for VAS craving assessment only)

- T-15: within 15 minutes prior to T_0

After T_0: (for VAS craving and VAS liking assessment) with a time window as indicated in brackets

- T1 after 4 minutes (± 1 minute)
- T2 after 10 minutes (± 1 minute)
- T3 after 15 minutes (± 1 minute)
- T4 after 30 minutes (± 2 minutes)
- T5 after 1 hour (± 5 minutes)
- T6 after 2 hours (± 5 minutes)
- T7 after 4 hours (± 5 minutes)
- T8 after 10 hours (± 5 minutes)

Additional subjective effects will be assessed on Day 1 to Day 3 by the ABOUT-Product experience questionnaire administered within 1 to 2 hours after T_0.

On Day 2, additional blood samples will be taken for determination of the nicotine concentration to evaluate terminal elimination half-life (t1/2z) in relation to T_0 from Day 2 at the following time points with a time window as indicated in brackets:

- T1z after 8 hours (± 5 minutes) after T_0 from Day 2
- T2z after 12 hours (± 5 minutes) after T_0 from Day 2
- T3z after 16 hours (± 10 minutes) after T_0 from Day 2
- T4z after 20 hours (± 10 minutes) after T_0 from Day 2

After enrollment at Day -1, the use of any other tobacco and nicotine containing products different from the product assigned for 6 minutes *ad libitum* use on Day 1 to Day 3, will not be allowed. Use of tobacco and nicotine containing products will not be restricted after the subject has been discharged from the investigational site on Day 3.

After discharge at Day 3, the subjects will enter a 3-day Safety Follow-Up Period (FU Period) during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs ongoing at discharge will be conducted by the investigational site.

Subjects who will be discontinued from the study before enrollment will be replaced. After enrollment but before randomization, subjects who will be discontinued from the study will enter the 3-day Safety Follow-Up Period and will be replaced. However, subjects that are discontinued after randomization will not be replaced.

3.2 Selection of Study Population

Thirty-six (36) subjects will be randomized to one of six possible product use sequences at Day 1.

The study population will be stratified by sex. Each sex will have a quota applied to ensure they represent at least 40% of the total randomized subjects.

In addition, at least 15% subjects of Black, Asian, American Indian or Alaska native, Native Hawaiian, other Pacific Islander race will be randomized to account for the US American smoking population. The randomization of subjects by ethnicity will not be enforced by stratification.

3.2.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria can be enrolled into the study:

Inclusion Criteria	Screening	Admission (Day -1)
1. Subject has signed the ICF and is able to understand the information provided in the ICF.	X	
2. Smoking male or female aged between 24 and 65 years old.	X	
3. Subject has smoked continuously for at least the last 3 years prior to the Screening visit.	X	
4. Subjects has smoked ≥ 10 commercially available cigarettes per day for 4 weeks prior to Screening Visit and Admission. Smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).	X	X
5. Subject does not plan to quit smoking cigarettes or using other nicotine or tobacco-containing products in the next 3 months.	X	X
6. Smoking, healthy subject as judged by the Investigator or designee based on available assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, and medical history).	X	

Inclusion Criteria	Screening	Admission (Day -1)
7. Subject is available for the entire study period and willing to comply with study procedures, including product use assignments, and periods of abstinence from any nicotine/tobacco containing products.	X	X

3.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria must not be enrolled into the study:

Exclusion Criteria	Screening	Admission (Day -1)
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).	X	
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners, or subjects who are involuntarily incarcerated).	X	
3. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease) or any other medical condition (including safety laboratory as per CTCAE), which as per the judgment of the Investigator would jeopardize the safety of the subject.	X	
4. As per the Investigator's judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.	X	
5. Subject has donated or received whole blood or blood products within 3 months prior to Screening Visit.	X	
6. BMI < 18.5 kg/m^2 or > 35.0 kg/m^2.	X	

Exclusion Criteria	Screening	Admission (Day -1)
7. Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission, whichever is longer, which has an impact on CYP2A6 activity.		X
8. Subject has a positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C or SARS-CoV-2.	X	
9. Subject has a history of alcohol abuse that could interfere with the subject's participation in study.	X	
10. Subject has a positive urine drug test. If positive for cannabinoids, inclusion will be at the discretion of the Investigator.	X	X
11. Subject has a positive alcohol breath test.	X	X
12. Subject or one of their family members [a] is a current or former employee of the tobacco industry.	X	
13. Subject or one of their family members [a] is employee of the investigational site or of any other parties involved in the study.	X	
14. Subject has participated in another clinical study within 3 months prior to the Screening Visit.	X	
15. Subject has been previously screened or enrolled in this study.	X	
16. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding.	X	X
17. For women of childbearing potential only [b]: subject does not agree to use an acceptable method of effective contraception [c].	X	X
18. Use of estrogen-containing hormonal contraception or hormone replacement therapy.	X	X

a. As defined by FDA guidance on Human Subject Protection (21 CFR 50.3(l), (m), 50.24(a)(6), (a)(7)(v), b)): "Family member" means among other things "parent", "spouse", "brothers, sisters, and spouses of brothers and sisters" and "any individual related by affinity…whose close association with the subject is equivalent of a family relationship."

b. Women who are not of childbearing potential meet at least one of the following criteria:
   - Have undergone hysterectomy or bilateral tubal ligation,
   - Have primary ovarian insufficiency, or
   - Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).

c. Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-Up Period.

3.3 Discontinuation of Subjects from the Study

Discontinued subjects will include both, subjects who withdraw from the study (subject's decision) and subjects who are discontinued from the study by the decision of the Investigator. A subject can only be discontinued from the study after enrollment.

Subjects will be informed that they are free to withdraw from the study at any time. Subjects will be questioned for the reason for withdrawal from the study, although they are not obliged to disclose it. If a subject withdraws from the study, he/she will be asked to confirm that he/she agrees to undertake the early termination procedures for safety assessments, and this information will be fully documented by the Investigator.

The subject will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed, unless the subject disagrees in writing.

When a subject is discontinued from the study, all early termination procedures (study protocol Section 9.7) will be performed unless the subject refuses to perform the assessments or the procedures have already been performed during the study day. Early termination procedures are to be performed only for subjects who have been exposed to P4M3 Gen 2.0. After the date of termination, the subject will enter into the 3-day Safety Follow-Up Period. This applies to all subjects independent of the reason of discontinuation (for example, withdrawal of consent, or at the Investigator's decision, etc.).

Subjects must be discontinued from the study for any of the following reasons:

- Withdrawal of informed consent.
- Any AE/SAE or condition (including clinically significant changes in a laboratory parameter), which at the discretion of the Investigator is not compatible with the subject's continued participation in this study.
- Positive pregnancy test (study protocol Section 8.5).
- If the Sponsor decides to prematurely terminate the study, the subject will be promptly informed by the Investigator. The Investigator should report the fact and the reason in writing to the IRB.
- Discontinuation is considered to be in the best interest of the subject or the other subjects as judged by the Investigator.

- Subject is not willing and/or ready to use P4M3 Gen 2.0 after the product test at Admission (Day -1). In such a situation, the subject will be discontinued after the product test and will enter the 3-day Safety Follow-up.
- Subject uses any tobacco or nicotine-containing product different from the assigned product during confinement.

Subjects may be discontinued from the study for the following reasons:

- Non-compliance to the study procedures based on the judgment of the Investigator.
- A sufficient number of subjects are already randomized to the study sequences (study protocol Section 5.2). In this case, additional subjects (alternates) will be discontinued prior to randomization.
- Violations of eligibility criteria have been determined (study protocol Section 5.4).

Subjects who will be discontinued from the study before enrollment will be replaced. After enrollment but before randomization, subjects who will be discontinued from the study will enter the 3-day Safety Follow-Up Period and will be replaced. However, subjects discontinued after randomization will not be replaced.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Populations will be described on the screened population.

Demographics, baseline characteristics, pharmacokinetics endpoints, pharmacodynamics endpoints, human puffing topography parameters, amount of nicotine delivered, will be analyzed using the PK population.

Safety will be analyzed using the safety population.

4.1.1 Screened Population

The screened population consists of all subjects who underwent screening.

4.1.2 Safety Population

The safety population is a subset of the screened population and consists of all subjects who give informed consent, have at least one exposure to P4M3 Gen 2.0, including the product test at Admission (Day -1), and have at least one safety assessment.

4.1.3 Pharmacokinetic Population

The Pharmacokinetic (PK) Population is a subset of the safety population and consists of all randomized subjects for whom at least one nicotine PK parameter can be derived. Only subjects without major protocol deviations, as defined in Section 4.2.1.1, which have an impact on evaluability of the main objective will be included in the PK population.

4.2 Protocol Deviations

Protocol deviations are defined as any departure from the procedures defined in the study protocol, including, but not limited to, any violation of inclusion/exclusion criteria, mis-randomization, use of any nicotine or tobacco-containing product other than the assigned product during the exposure period, assessments not performed or performed outside the scheduled time windows, or use of medications that are known to affect study endpoints.

4.2.1 Data Collection

Protocol deviations will be entered into the clinical trial management system (CTMS) or other approved format. The data collected in the CRF may be used to assess protocol deviations from the data programmatically. Protocol deviations will be reconciled and categorized prior to locking the clinical database as described in the data management plan (DMP).

All deviations will be reviewed to determine their impact when subjects are assigned to analysis populations. Each deviation will be classified as major or minor.

4.2.1.1 Major Protocol Deviations

Subjects with major protocol deviations will be identified (at a population level) to determine whether they will be excluded from any of the analysis populations.

Major deviations will include but are not limited to the deviations presented in Table 1.

Table 1 - Definition of Major Protocol Deviation Categories

Sub-Category	Description
Violation	Violation of inclusion/exclusion criteria
Mis-randomization	Violation of the product allocation process, including but not limited to the misclassification of subject's sex at randomization and incorrect product administered according to randomized sequence
Mis-use of product	Use of any nicotine or tobacco–containing product other than the assigned product during the exposure period, or use of any nicotine tobacco-containing product during at least 10 hours of abstinence from any nicotine/tobacco containing products (nicotine wash-out). Product use not compliant with planned regimen
Concomitant medications	Use of any drugs which are known to affect CYP2A6 activity

Among the eligibility criteria, violations of inclusion criteria 1, 2, 3, 4 and 7, or of the exclusion criteria 2 and 15 will be considered as impacting the evaluability or integrity of the primary objective. Other major protocol deviations will be assessed for their impact on the evaluability of the primary objective during the pre-analysis data review meeting.

4.2.1.2 Minor Protocol Deviations

Minor deviations will include, but are not limited to, the deviations presented in Table 2.

Table 2 - Definition of Minor Protocol Deviation Categories

Sub-Category	Description
Procedural violation	Violation of any study procedures not affecting safety or data evaluability
Time deviation (Plasma nicotine PK sample)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Section 4.2.1.3)
Time deviation (other assessment)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Section 4.2.1.3)
Assessment missing (Plasma nicotine PK sample)	Assessment is missing
Assessment missing (other assessment)	Assessment is missing
Randomization sequence	Subject randomized not according to the sequence of the subject numbers assigned during the screening visit

4.2.1.3 Assessment Time Points and Assessment Time Windows

Table 3 – Definition of Collection Time Points and Assessment Time Windows

Assessment	Nominal Time point(s) (relative to T_0)	Time Window
Plasma nicotine PK samples	5 minutes prior to T_0	± 1 minute
	1 minute after T_0	+ 30 seconds
	2 minutes after T_0	+ 1 minute
	4 minutes after T_0	+ 1 minute
	6 minutes after T_0	+ 1 minute
	8 minutes after T_0	+ 1 minute
	10 minutes after T_0	+ 1 minute
	12 minutes after T_0	+ 1 minutes
	15 minutes after T_0	± 2 minutes
	30 minutes after T_0	± 2 minutes
	1 hour after T_0	± 5 minutes
	2 hours after T_0	± 5 minutes
	4 hours after T_0	± 5 minutes
	10 hours after T_0	± 5 minutes
	24 hours after T_0	± 10 minutes
ABOUT-Product experience	On Days 1, 2, and 3	Within 60 to 120 minutes after T_0
VAS craving and liking assessment	15 minutes prior to T_0 (for craving only)	Within 15 minutes
	4 minutes after T_0	± 1 minute
	10 minutes after T_0	± 1 minute

Assessment	Nominal Time point(s) (relative to T_0)	Time Window
	15 minutes after T_0	± 1 minute
	30 minutes after T_0	± 2 minutes
	1 hour after T_0	± 5 minutes
	2 hours after T_0	± 5 minutes
	4 hours after T_0	± 5 minutes
	10 hours after T_0	± 5 minutes
Blood samples for λ_z	T1z after 8 hours	± 5 minutes
	T2z after 12 hours	± 5 minutes
	T3z after 16 hours	± 10 minutes
	T4z after 20 hours	± 10 minutes
ECG	Screening	Not applicable
	Day -1	Not applicable
	Days 1, 2, and 3	60 minutes ± 10 minutes after T_0
		60 to 120 minutes after T_0
	Day 4	Not applicable
	Early Termination	Not applicable
Weight of P4M3 Gen 2.0 Cartridges	Days 1, 2, and 3	Before T_0
		Within 120 min after T_0
Vital signs	Screening	Not applicable
	Day -1	Not applicable
	Days 1, 2, and 3	Before T_0
	Day 4	Not applicable
	Early Termination	Not applicable

4.2.2 Data Summarization

The number and percent of subjects with protocol deviations, and the number of protocol deviations, will be summarized. Summaries will be broken down by main deviation category (major/minor), sub-categories, and evaluability impact. Subjects will be counted once per deviation category, and can be counted for more than one deviation category.

4.3 Preliminary Data and Interim Analysis

There will be no interim analysis of this study data.

5. PRODUCT DESCRIPTIONS

5.1 Test Product

P4M3 Gen 2.0 is an ENDS or electronic cigarette (e-cigarette), which produces an aerosol through vaporization of an e-liquid. P4M3 Gen 2.0 is composed of a Battery unit containing all the control electronics with the rechargeable battery and a disposable Cartridge containing the e-liquid and the heating element. The Battery unit comprises several functions. The device provides electrical power when required, which is activated by puff detection. The device has a "dry mesh detection" function to prevent overheating when the liquid on heater is not sufficient.

The Battery unit is charged via a USB port. The Battery unit also features a tactile function that will operate when the unit is turned on and off and when a puff is taken.

The Battery unit is controlled through a single multi-function button used for switching on and off and allowing the modification of both the haptic (vibration) and the power level. The Cartridge consists of a reservoir for storing the e-liquid, which also acts as the mouthpiece and includes the air flow channels to carry the aerosol from the heater to the user. The Cartridge contains the e-liquid, the mesh heater sub-assembly and the porous materials for liquid retention and transport from the reservoir to the heater. The Cartridge is disposed of when the e-liquid in the reservoir is depleted.

The P4M3 Gen 2.0 e-liquid formulations are composed of propylene glycol (PG), vegetable glycerin (VG), water, tobacco-derived nicotine, lactic acid, benzoic acid and could differ in flavors and nicotine concentrations. The following P4M3 Gen 2.0 e-liquid formulations (variants) will be investigated in this study (Table 5.1).

Table 5.1 P4M3 Gen 2.0 variants

Name	Name in the study	Nicotine concentration	e-liquid flavor
P4M3 Gen 2.0 Classic Auburn	CA35	3.5 %	Tobacco
P4M3 Gen 2.0 Classic Menthol	CM35	3.5 %	Menthol

5.2 Reference Product

Subject's own cigarettes (Cigarettes) will be used as a comparator.

Subjects' preferred brand of commercially available, regular or mentholated cigarettes will not be provided by the Sponsor.

All eligible subjects will be asked to purchase their usual brand of cigarettes prior to Admission (Day -1). Every subject needs to bring his/her pack of unopened, single-brand cigarettes.

6. PHARMACOKINETICS

6.1 Collection Schedule for Plasma Nicotine

Collection schedule is described in Table 6.1.

Table 6.1 Plasma Nicotine Samples Collection Schedule

Day 1 (15 blood samples)	Prior to the start of product use (T0) 5 minutes ± 1 minute (T-1). In relation to T0 from Day 1: T1 after 1 minute + 30 seconds, T2 after 2 minutes + 1 minute, T3 after 4 minutes + 1 minute, T4 after 6 minutes + 1 minute, T5 after 8 minutes + 1 minute, T6 after 10 minutes + 1 minutes, T7 after 12 minutes + 1 minute, T8 after 15 minutes ± 2 minutes, T9 after 30 minutes ± 2 minutes, T10 after 1 hour ± 5 minute, T11 after 2 hours ± 5 minutes, T12 after 4 hours ± 5 minutes, T13 after 10 hours ± 5 minutes and T14 after 24 hours ± 10 minutes (Days 1, 2). The sample T14 on Day 1 will also be used to determine the nicotine baseline concentration prior to T0 on Day 2.
Day 2 (14 blood samples)	Same time points as on Day 1, except time point T1. The sample T14 after T0 on Day 1 will also be used to determine the nicotine baseline concentration prior to T0 on Day 2 and similarly, T14 after T0 on Day 2 for nicotine baseline concentration prior to T0 on Day 3.
Day 3 (13 blood samples)	Same time points as on Day 2, except no sample T14 after T0 on Day 3.
Day 2 (4 blood samples)	Samples for determination of the terminal elimination half-life (t1/2z). In relation to T0 from Day 2: T1z after 8 hours ± 5 minutes, T2z after 12 hours ± 5 minutes, T3z after 16 hours ± 10 minutes and T4z after 20 hours ± 10 minutes.

6.2 Plasma Nicotine Concentrations

Analytical Laboratory

Samples will be analyzed for nicotine in plasma using a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) detection analytical method with the appropriate quality controls in accordance with the Food and Drug Administration (FDA) Guidance for Industry: Bioanalytical Method Validation (May, 2001) and in accordance with FDA Good Laboratory Practice regulations (Title 21 CFR Part 58) at [redacted] Bioanalytical Services Lincoln, Nebraska.

In general, values below the lower limit of quantification (LLOQ) will be imputed using 0.5 x lower limit of quantification. For values above the upper limit of quantification (ULOQ), the ULOQ will be used for calculation and reporting in summary tables.

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

6.3 Plasma Nicotine Pharmacokinetic Parameters

Nicotine PK endpoints will be derived from the background-corrected plasma nicotine concentrations. Nicotine PK parameters will be derived from background-corrected plasma nicotine concentration versus time data using a non-compartmental analysis (NCA) technique using appropriate and validated PK software (e.g., Phoenix WinNonlin version 7.0 or higher).

For nicotine concentrations below the LLOQ (BLQ) for the calculation of descriptive statistics of observed plasma nicotine concentrations:

- BLQ values before T0 will be imputed by LLOQ/2.
- BLQ values after the last quantifiable value are not included in the analysis (e.g., for the calculation of AUC).
- Any BLQ value (after T0 and before the last quantifiable value) would need to be queried* and, if confirmed, it will be imputed by LLOQ/2.

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

The number and percent of values below LLOQ or above ULOQ will be presented in each summary table.

To minimize the carry-over effect in the nicotine plasma PK parameters due to limited washout periods, the correction for background-concentration (baseline nicotine level obtained pre-use) will be applied to the concentration data. This correction will be implemented by calculating the nicotine exposure parameters using background-corrected concentration values as described below.

The nicotine terminal elimination rate constant λ_z (and $t_{1/2z}$) will be estimated from the Day 2 PK samples listed in Section 6.1 by using a linear regression on the log-transformed plasma nicotine concentration data. The regression analysis should contain data from at least 3 different time points in the terminal phase (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. The nicotine plasma background-corrected PK parameters will be derived by performing the non-compartmental analysis (NCA) on the background 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, cC_t is the corrected concentration at each time point, C_t is the observed concentration at each time point, C_0 is the pre-use baseline concentration, λ_z is the Day 2 terminal elimination rate constant, t is the actual time since start of product use, and t' is the actual time since the time of the pre-use baseline sample.

In particular, the following PK parameters will be derived from background-corrected nicotine levels following 6 minutes *ad libitum* use:

C_{max}	Maximum background-corrected plasma concentration. C_{max} will be reported as long as there is at least one quantifiable concentration post T_0.
T_{max}	Time to maximum background-corrected plasma nicotine concentration C_{max}.
$AUC_{0\text{-}2min}$	Area under the background-corrected plasma concentration-time curve from start of product use (T_0) to 2 minutes.
$AUC_{0\text{-}4min}$	Area under the background-corrected concentration-time curve from T_0 to 4 minutes.
$AUC_{0\text{-}Tmax}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to subject-specific time to maximum plasma concentration after T_0.
$AUC_{0\text{-}10h}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 10 hours.
$AUC_{0\text{-}last}$	Area under the background-corrected plasma nicotine concentration-time curve from T0 to the time of last quantifiable concentration.
$AUC_{0\text{-}infinity}$	Area under the background-corrected plasma nicotine concentration-time curve extrapolated from T0 to infinity.
$_{max}(C_t/t)_{\ t\in[0,Tmax]}$	Maximum rate of absorption expressed as the maximum of the ratio of background-corrected concentration at a specific time over this time, from T_0 (exclusive) to T_{max} (inclusive).

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

For calculation of λ_z from observed data (to be used for background correction), concentrations BLQ will be set to 0 for pre-administration and prior to the first measurable concentration, and set to missing after the last quantifiable concentration (if applicable).

The following steps will applied for the other PK parameters:

- Concentrations below the lower limit of quantitation (BLQ) will be set to ½ the lower limit of quantitation (LLOQ) except for any BLQ values after the last quantifiable concentration which will be set to missing.
- The formula for background correction will be applied.
- After the calculation, pre-product administration values will be assigned a value of zero in the analyses. All other values obtained will be reported as is even if these values are BLQ, except for any negative values, which will be set to zero.

6.4 Pharmacokinetic Data Summarization and Presentation

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

Plasma nicotine concentrations (observed and background-corrected,) λ_z (observed only) and other PK parameters (background corrected only) will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data (Missing, n (%)), arithmetic mean (Mean), standard deviation (SD), percent CV (CV%), standard error of the mean (SEM), 95% confidence interval (95%CI), minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Summaries will be further stratified by Sex.

In addition, geometric mean (Geo. Mean), 95% geometric confidence interval (Geo. 95% CI) and geometric CV (Geo. CV%) will be presented as well, as applicable.

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

Categorical variables will be summarized by frequency statistics (number and percentage).

For endpoints relating to sampling times (e.g., T_{max}) only median, Q1, Q3, minimum and maximum will be presented.

All analyses and summaries will be performed by product and overall.

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

The level of precision and rounding for the summary statistics listed in Section 14.1.5.

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

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

6.5 Statistical Analysis of PK Parameters

6.5.1 Main analysis

A mixed model analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed nicotine PK parameters $AUC_{0\text{-}2min}$, $AUC_{0\text{-}4min}$, $AUC_{0\text{-}Tmax}$, $AUC_{0\text{-}10h}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}infinity}$, $_{max}(C_t/t)_{t\in[0,Tmax]}$ and C_{max}.

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

The results of this analysis for each of are presented in terms of geometric least square ratios and 95% confidence intervals for the P4M3 Gen 2.0:Cigarettes ratio.

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

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

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

PROC MIXED data=< > method=REML;

class subject sequence period product;

model log(parameter) = sequence period product/ddfm=KR;

repeated product / subject=subject type=csh;

lsmeans product / pdiff=control("CC") cl alpha=0.05;

run;

6.5.2 Sensitivity Analysis

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

In case the plasma concentrations cannot be background-corrected in 2 or more subjects in a sequence a sensitivity analysis will be performed similarly to the main analysis, whereby

- If the subject's terminal elimination rate cannot be estimated it will be substituted by the average terminal elimination rate of the subjects having the same sex,
- If the uncorrected nicotine concentration at baseline is not available for the Period 2 or 3, it will be substituted by the extrapolation of the previous concentrations using the terminal elimination rate.

7. PHARMACODYNAMIC EFFECTS (SUBJECTIVE EFFECTS AND RELATED BEHAVIORAL ASSESSMENTS)

7.1 Data Collection

7.1.1 ABOUT-Product Experience Questionnaire

Product Experience will be assessed via a subject self-reported outcome measure at the time point described in Table 3, using the Assessment of Behavioral Outcomes related to Tobacco and nicotine products (ABOUT) - Product Experience questionnaire (Cappelleri et al, 2007), part of the ABOUT Toolbox.

The questionnaire consists of three multi-item scales and two single-item scales, arising from an adaptation and rewording of the modified cigarette evaluation questionnaire (mCEQ) to RRPs and the Product Evaluation Scale (Hatsukami, D.K., et al., 2013).

The questionnaire assesses the degree to which subjects experience the reinforcing effects of P4M3 Gen 2.0 with CA35 and CM 35 Cartridges and Cigarettes by measuring:

- Product satisfaction (satisfying, tastes good, enjoy the product): average of the response scores from questions 1, 2, and 12.
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger): average of the response scores from questions 4 to 8.
- Aversion (dizziness, nausea): average of the response scores from questions 9 and 10.
- Enjoyment of respiratory tract sensations (single-item assessment): response score from question 3.
- Craving reduction (single-item assessment): response score from question 11.

Subjects will be asked to assess the 12 items of the questionnaire on a 7-point scale, ranging from “not at all” to “extremely”.

Responses on the 7-point scales, where 1 = not at all and 7 = extremely, for each ABOUT questionnaire will be treated as a continuous variable and used to calculate the factor scores.

7.1.2 VAS Craving Assessment

Cigarette craving will be assessed using a 1 item self-reported craving VAS, asking subjects to rate craving for cigarettes (How strong is your craving for cigarettes?), on a 100 mm unipolar scale, ranging from 0 (no craving), to 100 (strong craving). On Day 1 to Day 3, VAS craving assessment will be collected at: Within 15 minutes prior to T_0, after T_0 at 4 minutes ± 1 minute, 10 minutes ± 1 minute, 15 minutes ± 1 minute, 30 minutes ± 2 minutes, 1 hour ± 5 minutes, 2 hours ± 5 minutes, 4 hours ± 5 minutes, 10 hours ± 5 minutes.

7.1.3 VAS Liking Assessment

Cigarette and P4M3 Gen 2.0 liking will be assessed using a one item self-reported liking VAS, asking subjects to rate liking for product (At this moment, my liking for this product is:) on a 100 mm bipolar scale, ranging from 0 (strong disliking), to 100 (strong liking), with a neutral middle point, as recommended in the FDA guidance for industry on abuse liability assessment. On Day 1 to Day 3, VAS liking assessment will be collected at the following time points: after T_0 at 4 minutes ± 1 minute, 10 minutes ± 1 minute, 15 minutes ± 1 minute, 30 minutes ± 2 minutes, 1 hour ± 5 minutes, 2 hours ± 5 minutes, 4 hours ± 5 minutes, 10 hours ± 5 minutes.

7.2 Data Summarization

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% confidence interval) of the ABOUT-Product Experience questionnaire subscale scores and VAS craving and VAS liking assessments will be provided by study product and time points, when applicable. Change from baseline (pre-product use) for VAS craving score will be summarized by study product and time point. Individual responses will be listed. Summaries will be further stratified by Sex.

7.3 Inferential Analysis

An analysis of covariance (ANCOVA) will be conducted by product use. The PK parameters will be transformed in the natural logarithmic scale. The model will include terms for sequence, period and product liking by the VAS-liking assessment. The effect of VAS-liking will be analyzed in different models with VAS-liking at T_1 (after 4 minutes), T_2 (after 10 minutes), and T_3 (after 15 minutes). The results of this analysis will be presented by product in terms of:

- The percentage of variance explained by product liking by the VAS-liking assessment.
- The standardized effect of product liking by the VAS-liking assessment on the endpoint, defined as the mean effect divided by the square root of its variance.

The ANCOVA analysis will be performed using the following SAS code:

PROC MIXED data=< > method=type3;

By product;

class subject sequence period;

model log(PK parameter) = sequence period liking_score/ddfm=KR solution;

run;

Another analysis of covariance (ANCOVA) will be conducted similarly to the above with the exception that it will be performed overall using mixed effects ANCOVA where the model will include, in addition, the subject as a categorical random effect to model the within subject correlations.

The same model will also be used to perform the analysis for human puffing topography parameters (total number of puffs, total puff volume, and total puff duration) to estimate the effect of VAS-liking score on the topography parameters.

8. HUMAN PUFFING TOPOGRAPHY

8.1 Data Collection

Human puffing topography (HPT) involves the measurement of each subject's unique way of using P4M3 Gen 2.0.

The MDEDR puffing topography device measures and records the flow rate and other per-puff parameters listed in Table 8.1.

Table 8.1 Human Puffing Topography Parameters Per-Puff

Description	Variable	Unit
Puff number	N_i	
Puff volume	V_i	mL
Puff duration	D_i	s
Average puff flow	Qm_i	mL/s
Peak flow	Qc_i	mL/s
Inter puff interval	I_i	s
Sum of I_i and D_i	DF_i	s
Peak flow position	$PosQc_i$	%

From the per-puff parameters, per-product experience parameters, representing average or total values per product, will be derived as in Table 8.2.

Table 8.2 Human Puffing Topography Parameters Per-Product Use Experience

Description	Variable	Formula	Unit
Total number of puffs	NPC	ΣN_i	
Total puff volume	TVOL	ΣV_i	mL
Average puff volume	$AvgV_i$	ΣV_i / NPC, i=1 ... NPC	mL
Average puff duration	$AvgD_i$	ΣD_i / NPC, i=1 ... NPC	s
Total puff duration	TD_i	ΣD_i	s
Average flow	$AvgQm_i$	ΣQm_i / NPC, i=1 … NPC	mL/s
Average peak flow	$AvgQc_i$	ΣQc_i / NPC, i=1 … NPC	mL/s
Total inter puff interval	TI_i	ΣI_i	s
Average inter puff interval	$AvgI_i$	ΣQc_i / NPC, i=1 … NPC	s
Total puffing duration	TDF_i	ΣDF_i	s
Puff Frequency	PFeq	$NPC/TDF_i/60$	

8.2 Data Summarization

Granular data (collected by puff) will be in a first step summarized for each subject for the parameters described in the formula in Table 8.2, before deriving the descriptive statistics using the following procedure:

- First, data are averaged to a by cigarette or by cartridge basis.
- Then those average data are averaged to a by subject basis.

- Finally, descriptive statistics are provided by regimen and product on those "by subject average".

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% confidence interval) of the puffing parameters will be provided by study product. Summaries will be further stratified by Sex. Individual values will be listed.

9. AMOUNT OF NICOTINE DELIVERED FROM P4M3 GEN 2.0

9.1 Data Collection

P4M3 Gen 2.0 Cartridges will be weighed before T_0 and within 120 min after T_0 at the time points described in Table 3 to estimate the amount of nicotine delivered during product use.

The weight will be determined with a scale with an accuracy of 1 mg.

The difference in the cartridge weight from pre product use and post product use will be calculated. The amount of nicotine delivery from P4M3 Gen 2.0 will be calculated by dividing the difference in the cartridge weight [mg] by the specific density of the e-liquid [1129.2 mg/mL] multiplied by the nicotine concentration [39.5 mg/mL].

9.2 Data Summarization

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% confidence interval) of the amount of nicotine delivered will be provided by study product. Summaries will be further stratified by Sex. Individual values will be listed.

10. 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.

10.1 Disposition of Subjects

Subjects will be summarized by number of subjects screened, enrolled, enrolled and exposed to P4M3 Gen 2.0, randomized, completed, and discontinued the study with discontinuation reasons.

10.2 Demographics

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

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

10.3 Tobacco/Nicotine-Containing Product Use History Questionnaire

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

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

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

10.4 Usual Brand Cigarettes Documentation

Subject's usual brand of cigarettes will be documented and frequency counts will be provided for categorical variables (brand, brand style, flavor, menthol capsule, and cigarette length) overall and further stratified by sex.

10.5 Fagerström Test for Nicotine Dependence (FTND)

Potential nicotine dependence will be assessed at the Screening Visit using the FTND in its revised version as updated in 2012 (Fagerström, K.O., 1978, Heatherton, T.F., et al., 1991).

The questionnaire consists of six questions, which have to be answered by the subject himself/herself. The total score obtained on the test permit the classification of nicotine dependence into three levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points) (Fagerström, K., et al., 2012).

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

10.6 Medical History

All Medical History and Concomitant Disease will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 24.0 and listed by subject.

10.7 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using MedDRA®, Version 24.0. AEs will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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

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 and overall. The number and percentage of subjects with AEs, SAEs (including deaths), and product events will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to product discontinuation, AEs leading to study discontinuation, AEs by relatedness to product exposure (including expectedness) and relatedness to study procedures, AEs by severity, and AE by action taken related to the product. Tabulations will be performed for both the number of subjects experiencing an event and the number of events. Subjects with product events will also be summarized.

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

10.8 Clinical Laboratory Tests (Clinical Chemistry, Hematology, Urinalysis)

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

Out-of-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 will be listed in the table.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by study day. Change from baseline will be summarized in a similar manner. Baseline is

defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected on Admission (Day -1). Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

10.9 Vital Signs

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

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

Descriptive statistics will be reported for vital signs measurements (blood pressure, pulse, respiration, and temperature) by period. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected on prior to T_0 on Day 1. Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

10.10 Electrocardiogram

An ECG will be recorded at Screening, Admission (Day -1), and at Day 3 or at early termination. The ECG testing will be performed as per the investigational site standard practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval, corrected by the ECG device according to Fridericia's formula [QTcF]. 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 period. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected at Admission (Day -1). Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

10.11 Prior and Concomitant Medications

All prior and concomitant medications will be listed by subject and product using Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization Drug Dictionary) Version

01 Mar 2021. Concomitant procedures recorded during the study will be listed by subject. Concomitant medications will be summarized using frequency count by product.

10.12 Physical Examination

A physical examination will be conducted at the Screening Visit, at Admission (Day -1) and at the Day of Discharge (Day 3) or at early termination. All data found in the CRF will be listed. Physical examination has to be assessed as normal, abnormal – clinically not significant, or abnormal – clinically significant. Change in physical examination from baseline will be discussed in the clinical study report.

10.13 Spirometry

Spirometry without bronchodilator will be performed at the Screening Visit, Day -1, and at Discharge (Day 3) or early termination in accordance with the 2019 guideline update of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry (Graham, B.L., et al., 2019). Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set.

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

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

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

10.14 Cytochrome P450 2A6 (CYP2A6) Activity

CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites. CYP2A6 activity will be measured in plasma using the metabolic molar ratio of trans-3'-hydroxycotinine/cotinine.

On Day -1, one blood sample will be collected for determination of CYP2A6 activity (cotinine and trans-3'-hydroxy-cotinine) prior to the P4M3 Gen 2.0 product test.

Individual results will be listed and descriptive statistics will be presented for the Safety population.

11. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

Per protocol, demographics, baseline characteristics, pharmacokinetics endpoints, pharmacodynamics endpoints, human puffing topography parameters, amount of nicotine

delivered, will be analyzed using the randomized and PK population. They will be analyzed only in the PK population. The randomized population will not be defined.

Where comparisons between CA35 and Cigarettes, and between CM35 and Cigarettes, are performed, the comparison between CA35 and CM35 will be performed additionally.

12. REFERENCES

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13. TABLES, FIGURES, AND LISTINGS

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

The following is a list of table and figure titles that will be included in Sections 10, 11, 12, and 15 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

Programmer note: Tables, Listings, and Figures Style Guide provided by the Philip Morris Products S.A., will be used for the format and presentation styles for tables, figures, and listings.

13.1 In-text Summary Tables and Figures (CSR Sections 10 to 12)

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 (Screened Population)

Table 2 Summary of Demographics and Baseline Characteristics (Safety Population)

Section 11:

Pharmacokinetics

Table 3 Summary of Background-Corrected Plasma Nicotine PK Parameters of P4M3 Gen 2.0 and Cigarettes (PK Population)

Table 4 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameters for P4M3 Gen 2.0 and Cigarettes (PK Population)

Table 5 Statistical Comparisons of Plasma Nicotine PK Parameter T_{max} for P4M3 Gen 2.0 and Cigarettes (PK Population)

Figure 1 Background-Corrected Plasma Nicotine Concentration-Time Profiles of P4M3 Gen 2.0 and Cigarettes (PK Population)

Figure 2 Background-Corrected Plasma Nicotine Concentration-Time Profiles of P4M3 Gen 2.0 and Cigarettes [truncated at 1 hour post-use] (PK Population)

Subjective Effects

Table 6 Summary of the Subscale Scores of the ABOUT - Product Experience Questionnaire (PK Population)

Table 7 Summary of VAS Craving Assessment (PK Population)

Table 8 Summary of VAS Liking Assessment (PK Population)

Human Puffing Topography

Table 9 Summary of Total Number of Puffs, Total Puff Volume and Total Puff Duration Human Puffing Topography Parameters for P4M3 Gen 2.0 (PK Population)

Product Use Behaviors

Table 10 Summary of Amount of Nicotine Delivered from P4M3 Gen 2.0 (PK Population)

15.2.1.3 Demographics

Table 15.2.1.3.1 Summary of Demographics and Other Baseline Characteristics (Safety Population)

Table 15.2.1.3.2 Summary of Demographic and Other Baseline Characteristics (PK Population)

Table 15.2.1.3.2.1 Summary of Demographic and Other Baseline Characteristics by Sex (PK Population)

15.2.1.4 Tobacco/Nicotine-Containing Product Use History

Table 15.2.1.4.1 Summary of Tobacco/Nicotine-Containing Product Use History (Safety Population)

Table 15.2.1.4.2 Summary of Tobacco/Nicotine-Containing Product Use History (PK Population)

Table 15.2.1.4.2.1 Summary of Tobacco/Nicotine-Containing Product Use History by Sex (PK Population)

15.2.1.5 Usual Brand Documentation

Table 15.2.1.5.1 Summary of Usual Brand Documentation (Safety Population)

Table 15.2.1.5.2 Summary of Usual Brand Documentation (PK Population)

Table 15.2.1.5.2.1 Summary of Usual Brand Documentation by Sex (PK Population)

15.2.1.6 Fagerström Test for Nicotine Dependence (FTND)

Table 15.2.1.6.1 Summary of FTND Score (Safety Population)

Table 15.2.1.6.2 Summary of FTND Score (PK Population)

Table 15.2.1.6.2.1 Summary of FTND Score by Sex (PK Population)

15.2.1.7 Cytochrome P450 2A6 (CYP2A6) Activity

Table 15.2.1.7.1 Summary of Cytochrome P450 2A6 (CYP2A6) Activity (Safety Population)

15.2.2 PK/PD Summary Tables

15.2.2.1 Pharmacokinetics

Table 15.2.2.1.1 Summary of Background-Corrected Plasma Nicotine Concentrations by Product (PK Population)

Table 15.2.2.1.1.1 Summary of Background-Corrected Plasma Nicotine Concentrations by Product by Sex (PK Population)

Table 15.2.2.1.2 Summary of Observed Plasma Nicotine Concentrations by Product (PK Population)

Table 15.2.2.1.2.1 Summary of Observed Plasma Nicotine Concentrations by Product by Sex (PK Population)

Table 15.2.2.1.3 Summary of Background-Corrected Plasma Nicotine PK Parameters by Product (PK Population)

Table 15.2.2.1.3.1 Summary of Background-Corrected Plasma Nicotine PK Parameters by Product by Sex (PK Population)

Table 15.2.2.1.4 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameters for P4M3 Gen 2.0 Versus Cigarettes (PK Population)

Table 15.2.2.1.4.1 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameters for P4M3 Gen 2.0 Versus Cigarettes by Sex (PK Population)

Table 15.2.2.1.5 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameter T_{max} for P4M3 Gen 2.0 Versus Cigarettes Following Ad Libitum Use (PK Population)

Table 15.2.2.1.5.1 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameter T_{max} for P4M3 Gen 2.0 Versus Cigarettes Following Ad Libitum Use by Sex (PK Population)

15.2.2.2 Subjective Measurement Tables

Table 15.2.2.2.1 Summary of the Subscales of ABOUT - Product Experience Questionnaire (PK Population)

Table 15.2.2.2.1.1 Summary of the Subscales of ABOUT - Product Experience Questionnaire by Sex (PK Population)

Table 15.2.2.2.2 Summary of VAS Craving Assessment (PK Population)

Table 15.2.2.2.2.1 Summary of VAS Craving Assessment by Sex (PK Population)

15.2.3.6 Spirometry

Table 15.2.3.6.1 Summary of Spirometry and Change from Baseline (Safety Population)

13.3 Subject 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.

15.3.1 Subject Eligibility, Demographic Data, Baseline Characteristics

Listing 15.3.1.1 Subject information (Screened Population)

Listing 15.3.1.2 Subject Eligibility (Screened Population)

Listing 15.3.1.3 Subject Enrollment (Safety Population)

Listing 15.3.1.4 Demographics (Safety Population)

Listing 15.3.1.5 Physical Examination (Safety Population)

Listing 15.3.1.6 Medical History (Safety Population)

Listing 15.3.1.7 Tobacco/Nicotine-Containing Product Use History Questionnaire (Safety Population)

Listing 15.3.1.8 Usual Brand Documentation (Safety Population)

Listing 15.3.1.9 Fagerström Test for Nicotine Dependence (Safety Population)

Listing 15.3.1.10 Subject Discontinuation (Safety Population)

Listing 15.3.1.11 Protocol Deviations (Safety Population)

15.3.2 Product Use

Listing 15.3.2.1 Product Demonstration (Safety Population)

Listing 15.3.2.2 P4M3 Gen 2.0 Product Test (Day -1) (Safety Population)

Listing 15.3.2.3 Randomization (Safety Population)

Listing 15.3.2.4 Product Use (Safety Population)

15.3.4.2 Adverse Events

Listing 15.3.4.2.1 Adverse Events (Safety Population)

Listing 15.3.4.2.2 Details for Serious Adverse Events (Safety Population)

Listing 15.3.4.2.3 Product Malfunctions, Misuses and Subject Complaints (Safety Population)

Listing 15.3.4.2.4 MDEDR Malfunction (Safety Population)

15.3.4.3 Clinical Laboratory Assay

Listing 15.3.4.3.1 Clinical Laboratory Report - Clinical Chemistry (Safety Population)

Listing 15.3.4.3.2 Out-of-Range Values and Recheck Results – Clinical Chemistry (Safety Population)

Listing 15.3.4.3.3 Clinical Laboratory Report - Hematology (Safety Population)

Listing 15.3.4.3.4 Out-of-Range Values and Recheck Results – Hematology (Safety Population)

Listing 15.3.4.3.5 Clinical Laboratory Report - Urinalysis (Safety Population)

Listing 15.3.4.3.6 Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)

Listing 15.3.4.3.7 Clinically Significant Values and Recheck Results (Safety Population)

Listing 15.3.4.3.8 Alcohol Screen (Safety Population)

Listing 15.3.4.3.9 Drug Screen (Safety Population)

Listing 15.3.4.3.10 Urine Cotinine Screen (Safety Population)

Listing 15.3.4.3.11 Serology (HIV, HBsAg, HCV) (Safety Population)

Listing 15.3.4.3.12 Pregnancy (Safety Population)

Listing 15.3.4.3.13 Clinical Laboratory Reference Ranges

15.3.4.4 Vital Signs

Listing 15.3.4.4.1 Vital Signs (I of II) (Safety Population)

Listing 15.3.4.4.2 Vital Signs (II of II) (Safety Population)

Listing 15.4.1.1.2 Analysis SAS Output for Table 15.2.2.1.5

Listing 15.4.1.1.2.1 Analysis SAS Output for Table 15.2.2.1.5.1

Listing 15.4.1.1.3 Analysis SAS Output for Table 15.2.2.2.4

Listing 15.4.1.1.4 Analysis SAS Output for Table 15.2.2.2.5

Listing 15.4.1.1.5 Analysis SAS Output for Table 15.2.2.2.6

Listing 15.4.1.1.6 Analysis SAS Output for Table 15.2.2.2.7

13.5 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

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

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

16.1.9.2 Laboratory Certificates

16.1.9.3 Bioanalytical Reports

16.1.9.4 Bioanalytical References

16.1.10 Publications Based on the Clinical Study

16.1.11 All Publications Referenced in the Report

16.2 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.2.1 Case Report Forms for Deaths

16.2.2 Case Report Forms for Serious Adverse Events: Subject Number XXX

16.2.3 Withdrawals for Adverse Events

16.3 CRFs of All Study Subjects

16.3.1 Screen Failures

16.3.2 Enrolled and Not Randomized

16.3.3 Randomized

14. TABLE, FIGURE, AND LISTING SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. These tables will be generated from the [redacted] ADaM Version 2.1 data structure.

14.1 General TFL Specifications

14.1.1 Margins

The general document margins for both A4 and US Letter (8.5”X11”) size paper are defined in Table 14.1.

Table 14.1: 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.

14.1.2 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.

14.1.3 TFL Header/Footer Information

- **TFL Shells**

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

  Sponsor: "Philip Morris Products S.A."

  Protocol ID as specified in the Protocol "P4-PK-04-US"

  Status of the Document for post-text shells (i.e., Draft / Final)

  Version Number and Date

  The PMP S.A. logo will only be reported in the first page of the document.

- **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

  Statistical output listings = 15.4.X, with X matching the number of the corresponding analysis table (only used to report statistical output of models)

  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 of the post-text shells: Dry run – Draft – Final Draft – Final (others as needed). This will be noted in the TFL footer as: "Status: draft", or "Status: final", etc., as applicable.

In a footnote of each TFL, the analysis population definition will be included, when applicable:

- Screened Population = All subjects who underwent screening
- Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0, and have at least one safety assessment
- PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

14.1.4 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

Geo. CV% = Geometric Coefficient of Variation

SD = Standard Deviation

SEM = Standard Error of the Mean

Min = Minimum

Max = Maximum

Mean = Arithmetic Mean

Geo. Mean = Geometric Mean

Med = Median

95% CI = 95% Confidence Interval of the Arithmetic Mean

Geo. 95% CI = 95% Confidence Interval of the Geometric Mean

Q1 / Q3 = 1st and 3rd Quartile

BLQ = Below the Lower Limit of Quantification

ALQ = Above the Upper 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

Missing n(%) = number and percentage of values missing

14.1.5 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)

Continuous Variables will be presented with 3 significant digits, unless otherwise specified.

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+1 decimal places (unless otherwise stated)

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 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

14.2 In-text Summary Table Shells

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

Table 1 Subject Disposition Summary (Screened Population)

Disposition	Overall
Screened	X
Screen failure	X (X%[1])
Reason 1	X (X%[1])
Reason 2	X (X%[1])
Enrolled	X (X%[1])
Randomized	X (X%[2])
Not Randomized	X (X%[2])
Reason 1	X (X%[2])
Reason 2	X (X%[2])
Completed	X (X%[3])
Discontinued Early	X (X%[3])
Reason 1	X (X%[3])
Reason 2	X (X%[3])

[1] Percentages are expressed relative to the number of subjects screened
[2] Percentages are expressed relative to the number of subjects enrolled
[3] Percentages are expressed relative to the number of subjects randomized
Screened Population = All subjects who underwent screening
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 Summary Demographics and Baseline Characteristics (Safety Population)

Trait	Category/Statistics	Overall
Sex	Male	X (XX%)
	Female	X (XX%)
Race	Asian	X (XX%)
	Black or African American	X (XX%)
	White	X (XX%)
Ethnicity	Not Hispanic or Latino	X (XX%)
	Hispanic or Latino	X (XX%)
Age (yrs)	n	X
	Mean	XX.X
	SD	XX.XX
Weight (kg)	n	X
	Mean	XX.XX
	SD	XX.XXX
Height (cm)	n	X
	Mean	XXX.X
	SD	X.XX
BMI (kg/m²)	n	X
	Mean	XX.XXX
	SD	X.XXXX
Fagerström Score	n	X
	Mean	XX.XXX
	SD	X.XXXX
CYP2A6 Activity	n	X
	Mean	XXX.X
	SD	X.XX

SD = Standard deviation
BMI = Body mass index
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment.
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

In-text Table 3 will have the following format:

Table 3 Summary of Background-Corrected Plasma Nicotine PK Parameters of P4M3 Gen 2.0 and Cigarettes (PK Population)

PK Parameters	P4M3 Gen 2.0		Cigarettes
	CA35	CM35	
Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Param4 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]

CA35 = < >
CM35 = < >
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived
T_{max} values are presented as median (min, max).
Other parameters are presented as geometric mean, 95% geometric mean CISource: 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 PK parameters will be presented as specified in Section 6.3.
- n will be presented as an integer (with no decimal).
- If n is the same for all parameters in a column, it can be presented in the header row instead of in each row.
- In-text tables will show a reduced set of descriptive statistics as shown in the shell above.
- Geom CI will be presented to 2 decimals.

In-text Table 4 and post-text Table 15.2.2.1.4 will have the following format, and Table 15.2.2.1.4.1 a similar format:

Table 4 Statistical Comparisons of Background-Corrected Plasma Nicotine PK Parameters for P4M3 Gen 2.0 and Cigarettes (PK Population)

Parameter	Comparison (Test vs Reference)	Geometric LSMs		GMR (%)	95% Confidence Intervals	Intra-subject CV%
		Test (n)	Reference (n)			
C_{max}	CA35 vs Cigarettes	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
AUC*	CA35 vs Cigarettes	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
$_{max}(C_t/t)_{\ t\in[0,Tmax]}$	CA35 vs Cigarettes	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
C_{max}	CM35 vs Cigarettes	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
AUC*	CM35 vs Cigarettes	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
$_{max}(C_t/t)_{\ t\in[0,Tmax]}$	CM35 vs Cigarettes	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
C_{max}	CM35 vs CA35	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
AUC*	CM35 vs CA35	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX
$_{max}(C_t/t)_{\ t\in[0,Tmax]}$	CM35 vs CA35	X.XX (X)	X.XX (X)	XX.XX	X.XX – X.XX	X.XXX

CA35 = < >
CM35 = < >
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived
The first product in the comparison is the test and the second product in the comparison is the reference.
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:

* See Section 6.5 for the parameters to be included.

Presentation of Data:

- The following PK parameters will be presented in the following order and with the following units:
  - Table 4 and Table 15.2.2.1.4: C_{max} <ng/mL>, AUCs <ng*min/mL>, $_{max}(C_t/t)_{t\in[0,Tmax]}$ <ng/mL/min>
- n will be presented as an integer (with no decimal).
- See Section 6.4 for statistic presentation.

In-Text Table 5 and post-text Table 15.2.2.1.5 will have the following format, and Table 15.2.2.1.5.1 a similar format:

Table 5 Statistical Comparisons of Plasma Nicotine PK Parameter T_{max} for P4M3 Gen 2.0 and Cigarettes (PK Population)

		Test	Reference	-----Difference Test – Reference-----	
Parameter	Comparison (Test vs Reference)	Median (n)	Median (n)	Median	95% Confidence Interval
T_{max}	CA35 vs Cigarette	X.XX (X)	X.XX (X)	X.XX	X.XXXX - X.XXXX
T_{max}	CM35 vs Cigarette	X.XX (X)	X.XX (X)	X.XX	X.XXXX - X.XXXX
T_{max}	CM35 vs CA35	X.XX (X)	X.XX (X)	X.XX	X.XXXX - X.XXXX

CA35 = < >
CM35 = < >
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived
For the difference calculation, the first product in the comparison is the test and the second product in the comparison is the reference.
The 95% confidence interval is constructed using Walsh Averages and appropriate quantile on the normal approximation of the Wilcoxon Signed Rank test statistic.
Median is the point estimate of the Hodges-Lehmann median difference.

Notes for Generating the Actual Table:

Presentation of Data:

- See Section 6.4 for data presentation.

In-text Table 6 will have the following format:

Table 6 Summary of the Subscale Scores of the ABOUT-Product Experience Questionnaire (PK Population)

Subscale	P4M3 Gen 2.0		Cigarettes
	CA35	CM35	
Product satisfaction	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Psychological rewards	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Aversion	XXX.X (XX.X)] [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Enjoyment of respiratory tract sensations	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Craving reduction	XXX.X (XX.X) [n=xx]	XXX.X (XX.X)] [n=xx]	XXX.X (XX.X) [n=xx]

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived
Results are presented as arithmetic mean (± SD).
Source: Table XXXX
Program: /CAXXXXX/sas_prg/pksas/program name.sas DDMMMYYYY HH:MM

Programmer note: If n is the same for all values per column, it can be presented once in the header instead.

In-text Tables 7-8 will have the following format:

Table 7 Summary of VAS Craving Assessment (PK Population)

Scheduled Timepoint	P4M3 Gen 2.0		Cigarettes
	CA35	CM35	
Pre-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
4 min Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
10 min Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
15 min Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
30 min Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
1 hr Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
2 hr Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
4 hr Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
10 hr Post-Product Use	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived
Results are presented as arithmetic mean (± SD).
Source: Table XXXX
Program: /CAXXXXX/sas_prg/pksas/program name.sas DDMMMYYYY HH:MM

Programmer note:
There will be no pre-product use for VAS liking (Table 8).

In-text Table 9 will have the following format:

Table 9 Summary of Total Number of Puffs, Total Puff Volume and Total Puff Duration Human Puffing Topography Parameters for P4M3 Gen 2.0 (PK Population)

Per Puff Parameter	P4M3 Gen 2.0	
	CA35	CM35
Total number of puffs	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Total puff volume (mL)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Total puff duration (s)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived
Results are presented as arithmetic mean (± SD).
Source: Table XXXX
Program: /CAXXXXX/sas_prg/pksas/program name.sas DDMMMYYYY HH:MM

In-text Table 10 will have the following format:

Table 10 Summary of Amount of Nicotine Delivered from P4M3 Gen 2.0 (PK Population)

P4M3 Gen 2.0 Amount of Nicotine Delivered (mg)	
CA35	**CM35**
XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
CA35 = P4M3 Gen 2.0 Classic Auburn CM35 = P4M3 Gen 2.0 Classic Menthol PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived Results are presented as arithmetic mean (± SD). Source: Table XXXX Program: /CAXXXXX/sas_prg/pksas/program name.sas DDMMMYYYY HH:MM	

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

Table 11 Summary of Adverse Events (Safety Population)

Adverse Events*	CA35 Test†	Study Product				Safety Follow-up#
		CA35†	CM35†	Cigarettes†	Overall†	
Number of Subjects used Study Product	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%)
Number of Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Severity						
Mild	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Moderate	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Severe	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Relatedness to Study Product						
Related	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Not related	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Relatedness to Study Procedures						
Related	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Not related	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Number of Subjects with SAEs	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA® Version 24.0.
†Adverse events are product-use emergent.
Adverse events occurred between discharge and end of study for the subject.
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

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

Table 12 Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population)

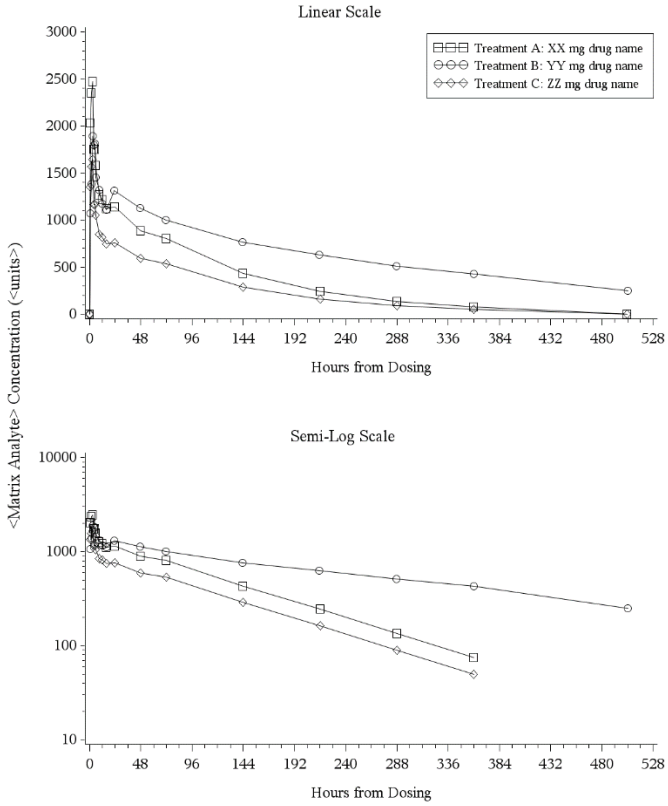
System Organ Class Preferred Term	CA35 Test† [n]	Study Product				Safety Follow-up# [n]
		CA35† [n]	CM35† [n]	Cigarettes† [n]	Overall† [n]	
Adverse Events (AE)	X (100%)	X (100%)	X (100%)	X (100%)	X (100%)	X (100%)
Gastrointestinal disorders	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Nausea	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Vomiting						
Dyspepsia	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
XXXXX	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Adverse events are classified according to MedDRA® Version 24.0.
†Adverse events are product-use emergent.
Adverse events occurred between discharge and end of study for the subject.
Source: Table XX.X.X
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_ae.sas DDMMMYYYY HH:MM

14.3 Figure Shells

In-text Figures 1 and 2 and post-text Figures 15.1.2.1.1 and 15.1.2.1.2, as well as post-text figures for individual profiles (Figures 15.1.2.1.3 and 15.1.2.1.4), will have the format shown below (both plots or only one per page, as applicable). In addition, Figures 15.1.2.2.1 through 15.1.2.2.3 will also be similar, but will have a line for each of the different variables.

Figure 1 Background-Corrected Plasma Nicotine Concentration-Time Profiles of P4M3 Gen 2.0 and Cigarettes (PK Population)



Notes for Generating the Actual Figure:

- For in-text mean graphs (Figures 1 and 2), present only one plot (linear); semi-log not needed.
- For graphs in Section 15, plot Geometric Mean with 95% Geometric CI for upper and lower error bars for summary plots (non-individual subject plots) and add footer "Geometric Mean ± 95% Geometric CI".
- Legend will be "Cigarettes", "CA35", and "CM35".
- X axis label will be "Time (minute)". Time can be expressed in hours if applicable.
- Y axis label will be "Plasma Nicotine Concentration (ng/mL)". If only one plot on page is presented, the label will be placed accordingly. There will be a separate y-axis label for each panel instead of a shared y-axis label in the graph when both linear and semi-log panels are presented.
- A footnote will read:
    - CA35 = P4M3 Gen 2.0 Classic Auburn
    - CM35 = P4M3 Gen 2.0 Classic Menthol
- Figures 2 and 15.1.2.1.2 will be truncated at 1 hour (60 minutes).
- Figures 15.1.2.2.1 through 15.1.2.2.3, in addition to the y-axis for the background corrected plasma nicotine concentration, will have an additional y-axis on the right side for the VAS scale for craving and liking. There will be three lines in these graphs as follows: concentration versus time, VAS craving score versus time, and VAS liking score versus time.

14.4 Summary Table Shells

Table 15.2.1.1.1 will have the following format:

Table 15.2.1.1.1 Summary of Disposition (Screened Population)

Category	Overall
Screened	XX
Screen failures	X (XX%[1])
<Reason>	X (XX%[1])
Enrolled	XX(XX%[1])
Not Randomized	XX (XX%[2])
<Reason>	X (XX%[2])
Randomized	XX (XX%[2])
Completed	XX (XX%[3])
Discontinued Early	X (XX%[3])
<Reason>	X (XX%[3])

Screened Population = All subjects who underwent screening
[1] Percentages are expressed relative to the number of subjects screened
[2] Percentages are expressed relative to the number of subjects enrolled
[3] Percentages are expressed relative to the number of subjects randomized
Program: /CAXXXXX/ECR/sas_prg/stsas/tab prog_name.sas DDMMMYYYY HH:MM Status: DRAFT (page X of Y)

Table 15.2.1.2.1 will be in the following format:

Table 15.2.1.2.1 Summary of Protocol Deviations (Safety Population)

Protocol Deviation	Admission	Study Product			Overall
		CA35	CM35	Cigarettes	
Number of Subjects with at least one deviation	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)
Number of Deviations	X (100%)	X (100%)	X (100%)	X (100%)	X (100%)
Minor	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Sub-category	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Major	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Sub-category	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Major without evaluability impact	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Major with evaluability impact	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
XXXXXXXXXXXXXXXXXXXXXXXX	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
XXXXXXXXXXXXXXXXXXXXXXXXX	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
XXXXXXXXXXXXXXXXXXXXXXXX	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
The denominator for percentage calculations is the total number of protocol deviations.
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_ae.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Tables 15.2.1.3.1 and 15.2.1.3.2 will have the same following format, and Table 15.2.1.3.2.1 a similar format:

Table 15.2.1.3.1 Summary of Demographics and Other Baseline Characteristics (Safety Population)

Trait		Overall
Sex	Male	X(XX.X%)
	Female	X(XX.X%)
Race	XXXXXXXXXX	X(XX.X%)
	XXXXX	X(XX.X%)
	XXXXX	X(XX.X%)
Ethnicity	Hispanic or Latino	X(XX.X%)
	Not Hispanic or Latino	X(XX.X%)
Age (yrs)	n	X
	Mean	X.X
	SD	X.XX
	CV%	X.X
	SEM	X.XX
	Minimum	XX
	Q1	X.X
	Median	X.X
	Q3	X.X
	Maximum	XX
	95% CI	XX-XX

SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /CAXXXXX/sas_prg/stsas/tab/ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer Note: Weight (kg), Height (cm), BMI (kg/m^2) and CYP2A6 will also be included in the demographic summary table.

Tables 15.2.1.4.1 and 15.2.1.4.2 will have the same following format, and Table 15.2.1.4.2.1 a similar format:

Table 15.2.1.4.1 Summary of Tobacco/Nicotine-containing Product Use History (Safety Population)

Question	Answer	Overall
1. Have you smoked continuously for the past 3 years?	Yes	X(XX.X%)
	No	X(XX.X%)
2. How many cigarettes have you smoked per day for the past four weeks?	n	X
	Mean	X.X
	SD	X.XX
	CV%	X.X
	SEM	X.XX
	Minimum	XX
	Q1	X.X
	Median	X.X
	Q3	X.X
	Maximum	XX
	95% CI	XX-XX

SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /CAXXXXX/sas_prg/stsas//tab/ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer Note: All questions in the nicotine/tobacco product use history will be included in the summary table.

Tables 15.2.1.5.1 and 15.2.1.5.2 will have the same following format, and Table 15.2.1.5.2.1 a similar format:

Table 15.2.1.5.1 Summary of Usual Brand Documentation (Safety Population)

Trait	Answer	Overall
Brand	XXXXXXXXXX	X(XX.X%)
	XXXXXXXXXXXXXX	X(XX.X%)
Flavor	Menthol	X(XX.X%)
	Non-menthol	X(XX.X%)

SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /CAXXXXX/sas_prg/stsas//tab/ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Tables 15.2.1.6.1 and 15.2.1.6.2 will have the same following format, and Table 15.2.1.6.2.1 a similar format:

Table 15.2.1.6.1 Summary of FTND Score (Safety Population)

FTND Trait	Answer	Overall
Fagerström Score	n	X
	Mean	X.X
	SD	X.XX
	CV%	X.X
	SEM	X.XX
	Minimum	XX
	Q1	X.X
	Median	X.X
	Q3	X.X
	Maximum	XX
	95% CI	XX-XX
Nicotine Dependence Level	Mild (1-3)	X(XX.X%)
	Moderate (4-6)	X(XX.X%)
	Severe (7-10)	X(XX.X%)

SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /CAXXXXX/sas_prg/stsas//tab/ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.1.7.1 will have the following format.

Table 15.2.1.7.1 Summary of Cytochrome P450 2A6 (CYP2A6) Activity (Safety Population)

Parameter (unit)	Statistic	Overall
Testname (unit)	n	X
	Mean	X.X
	SD	X.XX
	CV%	X.X
	SEM	X.XX
	Minimum	XX
	Q1	XX
	Median	X.X
	Q3	XX
	Maximum	XX
	95% CI	XX-XX

SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Tables 15.2.2.1.1 and 15.2.2.1.2 will have the following format, and Tables 15.2.2.1.1.1 and 15.2.2.1.2.1 a similar format:

Table 15.2.2.1.1 Summary of Background-Corrected Plasma Nicotine Concentrations by Product (PK Population)

		Product		
		P4M3 Gen 2.0		
Timepoint	Statistics	CA35	CM35	Cigarettes
XXX(min)	n	X	X	X
	Missing, n (%)	X(X.X%)	X(X.X%)	X(X.X%)
	BLQ, n (%)	X(X.X%)	X(X.X%)	X(X.X%)
	ALQ, n (%)	X(X.X%)	X(X.X%)	X(X.X%)
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	CV%	X.X	X.X	X.X
	SEM	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	XX-XX	XX-XX	XX-XX
	Geo. Mean	X.X	X.X	X.X
	Geo. CV%	X.X	X.X	X.X
	Geo. 95% CI	XX-XX	XX-XX	XX-XX

CA35 = < >
CM35 = < >
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile
CI = Confidence interval
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

Program: /CAXXXXX/sas_prg/pksas/ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

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

Table 15.2.2.1.3 will have the following format, and Table 15.2.2.1.3.1 a similar format:

Table 15.2.2.1.3 Summary of Background-Corrected Plasma Nicotine PK Parameters by Product (PK Population)

		Product		
		P4M3 Gen 2.0		
PK Parameters	Statistics	CA35	CM35	Cigarettes
XXX	n	X	X	X
	Missing, n (%)	X(X.X%)	X(X.X%)	X(X.X%)
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	CV%	X.X	X.X	X.X
	SEM	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	XX-XX	XX-XX	XX-XX
	Geo. Mean	X.X	X.X	X.X
	Geo. CV%	X.X	X.X	X.X
	Geo. 95% CI	XX-XX	XX-XX	XX-XX

CA35 = < >
CM35 = < >
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile
CI = Confidence interval
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

Program: /CAXXXXX/sas_prg/stsas/tab/ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

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

Table 15.2.2.2.1 will have the following format, and Table 15.2.2.2.1.1 a similar format:

Table 15.2.2.2.1 Summary of Subscale Scores of ABOUT - Product Experience Questionnaire (PK Population)

		Product		
		P4M3 Gen 2.0		
Subscale	Statistics	CA35	CM35	Cigarettes
Satisfaction	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	CV%	X.X	X.X	X.X
	SEM	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	XX-XX	XX-XX	XX-XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile
CI = Confidence interval
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

Program: /CAXXXXX/sas_prg/stsas/tab/ ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

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

Tables 15.2.2.2.2 and 15.2.2.2.3 will have the following format, and Tables 15.2.2.2.2.1 and 15.2.2.2.3.1 a similar format:

Table 15.2.2.2.2 Summary of VAS Craving Assessment (PK Population)

		Product		
		P4M3 Gen 2.0		
Scheduled Timepoint	Statistics	CA35	CM35	Cigarettes
Pre-Product Use	n	X	X	X
	Mean	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX
	CV%	X.X	X.X	X.X
	SEM	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX
	Q1	X.X	X.X	X.X
	Median	X.X	X.X	X.X
	Q3	X.X	X.X	X.X
	Maximum	XX	XX	XX
	95% CI	XX-XX	XX-XX	XX-XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile
CI = Confidence interval
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

Program: /CAXXXXX/sas_prg/stsas/tab/ ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

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

Tables 15.2.2.2.4 through 15.2.2.2.7 will have the following format:

Table 15.2.2.2.4 Inferential Analysis of VAS Liking Assessment on PK Parameters (PK Population)

Product	PK Parameter	Sum Square of Linking Score	Total Sum Square	Percentage*	Standardized Effect of Liking Score
CA35	XXXXX	XXXX	XXXX	XX.XX	XX
	XXXXX	XXXX	XXXX	XX.XX	XX
	XXXXX	XXXX	XXXX	XX.XX	XX
CM35	XXXXX	XXXX	XXXX	XX.XX	XX
	XXXXX	XXXX	XXXX	XX.XX	XX
	XXXXX	XXXX	XXXX	XX.XX	XX
Cigarettes	XXXXX	XXXX	XXXX	XX.XX	XX
	XXXXX	XXXX	XXXX	XX.XX	XX
	XXXXX	XXXX	XXXX	XX.XX	XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

Sum square of liking score and total sum square are from ANCOVA model.
*percentage = The percentage of variance explained by product liking by the VAS-liking assessment which calculated as Sum square of product liking score divided by total sum square and multiply 100.
Standardized effect of product liking is defined as the mean effect divided by the square root of its variance which is the t-value of the product liking score effect.
Program: /CAXXXXX/sas_prg/stsas/tab/ ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer Note: PK parameters (C_{max}, T_{max}, and $AUC_{0\text{-infinity}}$) and the human puffing topography parameters (total number of puffs, total puff volume, and total puff duration) to be included.

Table 15.2.2.3.1 will have the following format:

Table 15.2.2.3.1 Summary of Human Puffing Topography Parameters (PK Population)

		Product	
		P4M3 Gen 2.0	
Topography Parameter	Statistics	CA35	CM35
XXXXXXXX	n	X	X
	Mean	X.X	X.X
	SD	X.XX	X.XX
	CV%	X.X	X.X
	SEM	X.XX	X.XX
	Minimum	XX	XX
	Q1	X.X	X.X
	Median	X.X	X.X
	Q3	X.X	X.X
	Maximum	XX	XX
	95% CI	XX-XX	XX-XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile
CI = Confidence interval
Program: /CAXXXXX/sas_prg/stsas/tab/ ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer Note: All per-subject parameters (Table 15.2.2.3.1) will be included in the summary table.

Table 15.2.2.4.1 will have the following format:

Table 15.2.2.4.1 Summary of Amount of Nicotine Delivered from P4M3 Gen 2.0 and Number of Cigarettes Smoked (PK Population)

	P4M3 Gen 2.0 Amount of Nicotine Delivered (mg)		
Statistics	CA35	CM35	Subject's Own Cigarette Number of Cigarettes Smoked
n	X	X	X
Mean	X.X	X.X	X.X
SD	X.XX	X.XX	X.XX
CV%	X.X	X.X	X.X
SEM	X.XX	X.XX	X.XX
Minimum	XX	XX	XX
Q1	X.X	X.X	X.X
Median	X.X	X.X	X.X
Q3	X.X	X.X	X.X
Maximum	XX	XX	XX
95% CI	XX-XX	XX-XX	XX-XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol

PK Population = Subset of the safety population including all randomized subjects without major protocol deviations impacting the evaluability of the main objectives and for whom at least one nicotine PK parameter can be derived

SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile
CI = Confidence interval
Program: /CAXXXXX/sas_prg/stsas/tab/ ADaM_program_name.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.1.1 will have the following format:

Table 15.2.3.1.1 Summary of Adverse Events by Product (Safety Population)

	Study Product					
		P4M3 Gen 2.0				
Adverse Event*	CA35 Test† n (%) Events	CA35† n (%) Events	CM35† n (%) Events	Cigarettes† n (%) Events	Overall† n (%) Events	Safety Follow-up# n (%) Events
Number of Subjects Who Received Study Product	N=XX	N=XX	N=XX	N=XX	N=XX	N=XX
Number of Subjects With Adverse Events	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Serious AE (SAEs)	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Non-serious AEs	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Severity						
Mild	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Moderate	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Severe	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Related to study product						
Related	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Expected	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Not expected	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Not related	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Related to study procedure						
Related	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
Not related	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
AE leading to product discontinuation	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX
AE leading to study discontinuation	X (X%) XX	X (X%) XX	X (XX%) XX	X (X%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Adverse events occurred between discharge and end of study for the subject
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.1.2 will have the following format:

Table 15.2.3.1.2 Summary of Adverse Events by System Organ Class, Preferred Term, and Product (Safety Population)

	Study Product					
		P4M3 Gen 2.0				
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events	Safety Follow-up# N=XX n (%) Events
Any Adverse events	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Adverse events occurred between discharge and end of study for the subject

Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.1.3 will have the following format:

Table 15.2.3.1.3 Summary of Adverse Events by System Organ Class, Preferred Term, Product, and Relationship to Study Product Including Expectedness (Safety Population)

	Study Product					
		P4M3 Gen 2.0				
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events	Safety Follow-up# N=XX n (%) Events
Any Adverse events	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Related to IP	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Expected	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Unexpected	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Related to IP	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Expected	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Unexpected	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Unrelated to IP	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Adverse events occurred between discharge and end of study for the subject
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.1.4 will have the following format:

Table 15.2.3.1.4 Summary of Adverse Events by System Organ Class, Preferred Term, Product, and Relationship to Study Procedure (Safety Population)

	Study Product					
		P4M3 Gen 2.0				
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events	Safety Follow-up# N=XX n (%) Events
Adverse events (AE) related to study procedures	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Adverse events occurred between discharge and end of study for the subject
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.1.5 will have the following format:

Table 15.2.3.1.5 Summary of Adverse Events by System Organ Class, Preferred Term, Product, and Severity (Safety Population)

	Study Product					
		P4M3 Gen 2.0				
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events	Safety Follow-up# N=XX n (%) Events
Adverse Events	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Mild	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Moderate	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Severe	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Mild	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Moderate	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Severe	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Mild	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Moderate	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Severe	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Adverse events occurred between discharge and end of study for the subject
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.1.6 will have the following format:

Table 15.2.3.1.6 Summary of Adverse Events Leading to Product Discontinuation by System Organ Class, Preferred Term (Safety Population)

	Study Product				
		P4M3 Gen 2.0			
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events
Any Adverse Events leading to product discontinuation	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note; If there is no AE leading for product discontinuation, a note will be added to the table as "There were no AEs leading to product discontinuation during the study".

Table 15.2.3.1.7 will have the following format:

Table 15.2.3.1.7 Summary of Adverse Events Leading to Study Discontinuation by System Organ Class, Preferred Term, and Product (Safety Population)

	Study Product				
		P4M3 Gen 2.0			
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events
Any Adverse Events leading to study discontinuation	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: If there is no AE leading for study discontinuation, a note will be added to the table as "There were no AEs leading to study discontinuation during the study".

Table 15.2.3.1.8 will have the following format:

Table 15.2.3.1.8 Summary of Adverse Events With Action Taken Related to the Product by System Organ Class, Preferred Term, and Product (Safety Population)

	Study Product				
		P4M3 Gen 2.0			
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events
Adverse Events	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
No action taken	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Action taken for product	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
No action taken	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Action taken for product	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
No action taken	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Action taken for product	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
No action taken	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Action taken for product	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.1.9 will have the following format:

Table 15.2.3.1.9 Summary of Serious Adverse Events (Safety Population)

	Study Product					
		P4M3 Gen 2.0				
	CA35 Test†	CA35†	CM35†	Cigarettes†	Overall†	Safety Follow-up#
	N=XX	N=XX	N=XX	N=XX	N=XX	
	n (%) Events	n (%) Events	n (%) Events	n (%) Events	n (%) Events	n (%) Events
Serious Adverse Events	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Death	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Life threatening	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Hospitalization	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Disability	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Congenital anomaly	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Important medical event	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Severity						
Mild	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Moderate	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Severe	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Related to study product						
Related	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Unrelated	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Related to study Procedure						
Related	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Unrelated	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Adverse events occurred between discharge and end of study for the subject
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: If there are no SAEs, a note will be added to the table as "No serious adverse events were reported during the study".

Table 15.2.3.1.10 will have the following format:

Table 15.2.3.1.10 Summary of Serious Adverse Events by System Organ Class, Preferred Term, and Product (Safety Population)

	Study Product					
		P4M3 Gen 2.0				
System Organ Class Preferred Term	CA35 Test† N=XX n (%) Events	CA35† N=XX n (%) Events	CM35† N=XX n (%) Events	Cigarettes† N=XX n (%) Events	Overall† N=XX n (%) Events	Safety Follow-up# N=XX n (%) Events
Any Serious Adverse Events	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
SOC2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 1	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term 2	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX
Preferred term n	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX	X (XX%) XX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
*Adverse events are classified according to MedDRA Version 24.0
†Adverse events are product-use emergent
Adverse events occurred between discharge and end of study for the subject
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: If there are no SAEs, a note will be added to the table as "No serious adverse events were reported during the study".

Table 15.2.3.1.11 will have the following format:

Table 15.2.3.1.11 Summary of P4M3 Gen 2.0 Product Events and Malfunction/Misuse (Safety Population)

	P4M3 Gen 2.0		
Product Event	**CA35**	**CM35**	**Overall**
Number of Subjects Who Received Study Product	XX (100%)	XX (100%)	XX (100%)
Number of Subjects Reported Product Event	X (X%)	X (X%)	X (X%)
Break	X (X%)	X (X%)	X (X%)
Major	X (X%)	X (X%)	X (X%)
Minor	X (X%)	X (X%)	X (X%)
Fluid Leak	X (X%)	X (X%)	X (X%)
Major	X (X%)	X (X%)	X (X%)
Minor	X (X%)	X (X%)	X (X%)
Intermittent Loss of Power	X (X%)	X (X%)	X (X%)
Major	X (X%)	X (X%)	X (X%)
Minor	X (X%)	X (X%)	X (X%)
Power Problem	X (X%)	X (X%)	X (X%)
Major	X (X%)	X (X%)	X (X%)
Minor	X (X%)	X (X%)	X (X%)
Premature Indicator Activation	X (X%)	X (X%)	X (X%)
Major	X (X%)	X (X%)	X (X%)
Minor	X (X%)	X (X%)	X (X%)
Other	X (X%)	X (X%)	X (X%)
Major	X (X%)	X (X%)	X (X%)
Minor	X (X%)	X (X%)	X (X%)
Product events leading to AEs	X (X%)	X (X%)	X (X%)
Misuse	X (X%)	X (X%)	X (X%)

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Tables 15.2.3.2.2 and 15.2.3.2.3 will resemble Table 15.2.3.2.1

Table 15.2.3.2.1 Summary and Change from Baseline of Clinical Chemistry Parameters (Safety Population)

			Original Value			Change from Baseline
Laboratory Test (units)	Normal Range	Statistic	Screen	Admission Day -1	Discharge Day 3	Discharge Day 3
Testname (unit)	< - >#	n	X	X	X	X
		Mean	X.X*	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		CV%	X.X	X.X	X.X	X.X
		SEM	X.XX	XX.X	XX.X	XX.X
		Minimum	XX	XX	XX	XX
		Q1	X.X	X.X	X.X	X.X
		Median	X.X	X.X	X.X	X.X
		Q3	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX
		95% CI	XX-XX	XX-XX	XX-XX	XX-XX
Testname (unit)	< - >	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		CV%	X.X	X.X	X.X	X.X
		SEM	X.XX	XX.X	XX.X	XX.X
		Minimum	XX	XX	XX	XX
		Q3	X.X	X.X	X.X	X.X
		Median	X.X	X.X	X.X	X.X
		Q3	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX
		95% CI	XX-XX	XX-XX	XX-XX	XX-XX

= Lowest of the lower ranges and highest of the higher ranges are used. Refer to Listing 16.1.9.1 for the breakdown.
* Above Normal Range, ^ Below Normal Range
Baseline is the result closest and prior to the first product administration (Admission Day -1).
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0, and have at least one safety assessment
Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: Similar for remaining laboratory tests.

Table 15.2.3.3.1 will have the following format.

Table 15.2.3.3.1 Summary of Vital Signs and Change from Baseline (Safety Population)

Vital signs (units)	Time Point	Statistic	Original Value	Change from Baseline
Testname (unit)	Screen	n	X	
		Mean	X.X	
		SD	X.XX	
		CV%	X.X	
		SEM	X.XX	
		Minimum	XX	
		Q1	X.X	
		Median	X.X	
		Q3	X.X	
		Maximum	XX	
		95% CI	XX-XX	
	Day -1	n	X	
		Mean	X.X	
		SD	X.XX	
		CV%	X.X	
		SEM	X.XX	
		Minimum	XX	
		Q1	X.X	
		Median	X.X	
		Q3	X.X	
		Maximum	XX	
		95% CI	XX-XX	
Overall Results	Screen	Normal	X(XX%)	
		Abnormal NCS	X(XX%)	
		Abnormal CS	X(XX%)	

Baseline is the result closest and prior to the first product administration (Day 1).
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
NCS = Not clinically significant, CS = Clinically significant
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: Similar for remaining vital signs measurements. Change from baseline will be presented for the time points after Day 1. Overall results will be presented as frequency count and percentage by time point.

Table 15.2.3.4.1 will have the following format.

Table 15.2.3.4.1 Summary of 12-Lead Electrocardiogram and Change from Baseline (Safety Population)

		Original Value			Change from Baseline
Parameter (unit)	Statistic	Screen	Admission Day -1	Discharge Day 3	Discharge Day 3
Testname (unit)	n	X	X	X	X
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	CV%	X.X	X.X	X.X	X.X
	SEM	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Q1	X.X	X.X	X.X	X.X
	Median	X.X	X.X	X.X	X.X
	Q3	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX
	95% CI	XX-XX	XX-XX	XX-XX	XX-XX
Overall Interpretation	Normal	X(XX%)	X(XX%)	X(XX%)	
	Abnormal NCS	X(XX%)	X(XX%)	X(XX%)	
	Abnormal CS	X(XX%)	X(XX%)	X(XX%)	

Baseline is the result closest and prior to the first product administration (Admission Day -1).
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
NCS = Not clinically significant, CS = Clinically significant
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: Similar for remaining ECG parameters.

Table 15.2.3.5.1 will have the following format:

Table 15.2.3.5.1 Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 (Safety Population)

	Product			
Concomitant Medication*	**CA35**	**CM35**	**Cigarettes**	**Overall**
Number of Subjects Who Received Study Product	XX (100%)	XX (100%)	XX (100%)	XX (100%)
Number of Subjects Used Concomitant Medication	X (XX%)	X (XX%)	X (XX%)	X (XX%)
ATC1	X (X%)	X (X%)	X (X%)	X (X%)
ATC2	X (X%)	X (X%)	X (X%)	X (X%)

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
* Concomitant medication is classified according to WHO DD Version 01MAR2021.
Medication taken prior to the first product use and after discharge from CRU are not included in the analysis.
Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Table 15.2.3.6.1 will have the following format.

Table 15.2.3.6.1 Summary of Spirometry and Change from Baseline (Safety Population)

		Original Value			Change from Baseline
Parameter (unit)	Statistic	Screening	Admission (Day -1)	Discharge (Day 3)	Discharge (Day 3)
Testname (unit)	n	X	X	X	X
	Mean	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX
	CV%	X.X	X.X	X.X	X.X
	SEM	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Q1	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X
	Q3	XX	XX	XX	XX
	Maximum	XX	XX	XX	XX
	95% CI	XX-XX	XX-XX	XX-XX	XX-XX
Overall Result	Normal	X (XX%)	X (XX%)	X (XX%)	
	Abnormal NCS	X(XX%)	X(XX%)	X(XX%)	
	Abnormal CS	X(XX%)	X(XX%)	X(XX%)	

Baseline is the result closest and prior to the first product administration (Day -1).
SD = Standard deviation, CV% = Coefficient of variance, SEM = Standard error of mean, Q1 = 1st quartile, Q3 = 3rd quartile, CI = Confidence interval
NCS = Not clinically significant, CS = Clinically significant
Safety Population = All subjects who underwent screening, give informed consent, have at least one exposure to P4M3 Gen 2.0 and have at least one safety assessment
Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: Similar for remaining Spirometry parameters.

14.5 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 [redacted] SDTM Version 1.4 data structure.

Listing 15.3.1.1 Subject information (Screened Population)

Subject Number	Subject ID	Informed Consent Date	Informed Consent Time	Protocol Version	Re-Consent Version	Re-Consent Date	Re-Consent Time
X	X	DDMMMYYYY	HH:MM	XXXXXX	XXXXXX	DDMMMYYYY	HH:MM

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: Subject ID is subject identification including protocol information.

Listing 15.3.1.2 Subject Eligibility (Screened Population)

Subject Number	Study Period	Visit Date	Were all Eligibility Criteria Met?	Criteria Type	Criteria ID Not Met	Was the Subject Confirmed to be Eligible for the Study on Admission and Randomized?
X	Admission	DDMMMYYYY	XXX			XXX

Listing 15.3.1.3 Subject Enrollment (Safety Population)

Subject Number	Study Period	Was the Subject Enrolled?	Criteria Type	Criteria ID Not Met	If Other, Specify
X	Admission	XXX			

Listing 15.3.1.4 Demographics (Safety Population)

Subject Number	Visit Date	Year of Birth	Age (yrs)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m^2)
X	DDMMMYYYY	YYYY	XX	XXXX	XXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX
X	DDMMMYYYY	YYYY	XX	XXXX	XXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX
X	DDMMMYYYY	YYYY	XX	XXXX	XXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX
X	DDMMMYYYY	YYYY	XX	XXXX	XXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX
X	DDMMMYYYY	YYYY	XX	XXXX	XXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX
X	DDMMMYYYY	YYYY	XX	XXXX	XXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX
X	DDMMMYYYY	YYYY	XX	XXXX	XXXXX	XXXXXXXXXXX	XXX.X	XXX.X	XX.XX

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.1.5 Physical Examination (Safety Population)

Subject Number	Study Period	Date	Was PE Performed?	Reason for Not Done	Body System	If Other, Specify	Result	Specify if Clinically Significant or Not Done
X	Screening	D DMMMYYYY	XXX		XXXXX		XXXX	
					XXXXX		XXXX	XXXXXXXXXXXXX
					XXXXX		XXXX	

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.1.6 Medical History (Safety Population)

Subject Number	Any History?	Study Period	MH Number	Condition or Event	Start Date	End Date	Ongoing?	Preferred Term*
X	XXX	Screening	XX	XXXXX	DDMMM/YYYY	DDMMM/YYYY	XXX	XXXXXXXXXXX

Note: * Medical histories are classified according to the MedDRA Version 24.0.
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.1.7 Tobacco/Nicotine-Containing Product Use History Questionnaire (Safety Population)

Subject Number	Study Period	Was Questionnaire Completed?	If No, Reason For Not Done	Date	Question	Answer
X	Screening	XXX		DDMMMYYYY	XXXXXXXXXXXXXXXXXXXXXXXXXXX?	XXX
					XXXXXXXXXXXXXXXXXXXXXXXXXXX?	XX
					XXXXXXXXXXXXXXXXXXX?	XXX
					XXXXXXXXXXXXXXXXXXXXXXXXXXX?	XX

Listing 15.3.1.8 Usual Brand Documentation (Safety Population)

Subject Number	Study Period	Has Subject's Usual Brand Changed Since Last Reported?	Brand	If Other, Specify	Brand Style	If Other, Specify	Flavor	Menthol Capsule	Cigarette Length
X	Screening	XXX	XXXXX		XXXXX		XXXXXX	XXXXX	XXXXX

Listing 15.3.1.9 Fagerström Test for Nicotine Dependence (Safety Population)

Subject Number	Study Period	Was Assessment Completed?	Reason for Not Done	Date	Question*						Total Score	Classification of Nicotine Dependence
					1	2	3	4	5	6		
X	XXXX	XXX		DDMMMYYYY	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	X	XXXXXXXXXX

Note: * 1 = .How soon after you wake up do you smoke your first cigarette?
2 = Do you find it difficult to refrain from smoking in places where it is prohibited?
3 = Which cigarette would you hate most to give up?
4 = How many cigarettes per day do you smoke?
5 = Do you smoke more frequently during the first hours after awakening than during the rest of the day?
6 = Do you smoke even if you are so sick that you are in bed most of the day?
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.1.10 Subject Discontinuation (Safety Population)

Subject Number	Product Sequence	Date of Last Contact	Did the Subject Complete the Study?	If No, Reason for Discontinuation	Specify	Primary Adverse Event Term
X	X	DDMMMYYYY	XXX			
X	X	DDMMMYYYY	XXX	XXXXXX		

Sequence 1: CA35-Cigarettes-CM35
Sequence 2: CA35-CM35-Cigarettes
Sequence 3: Cigarettes-CA35-CM35
Sequence 4: Cigarettes-CM35-CA35
Sequence 5: CM35-Cigarettes-CA35
Sequence 6: CM35-CA35-Cigarettes
CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM- Status: DRAFT (Page X of Y)

Listing 15.3.1.11 Protocol Deviations (Safety Population)

Subject Number	Product Sequence	Date	Deviation	Code Term	Major/ Minor	Deviation Category
X	X	DDMMMYYYY	XXXXXXXXXXXXXXXXXXXXXXXX	XXXX	XXXXX	XXXXXXXX

Sequence 1: CA35-Cigarettes-CM35
Sequence 2: CA35-CM35-Cigarettes
Sequence 3: Cigarettes-CA35-CM35
Sequence 4: Cigarettes-CM35-CA35
Sequence 5: CM35-Cigarettes-CA35
Sequence 6: CM35-CA35-Cigarettes CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.2.1 Product Demonstration (Safety Population)

Subject Number	Study Period	Was a Product Demonstration Given?	If No, Reason For Not Done	Date
X	XXXX	XXX		DDMMMYYYY

Listing 15.3.2.2 P4M3 Gen 2.0 Product Test (Day -1) (Safety Population)

Subject Number	Study Period	Did Subject Participate in Product test?	If No, Reason For Not Done	Date of Test	Start Time	End Time
X	XXX	XXX		DDMMMYYYY	HH:MM	HH:MM

Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.2.3 Randomization (Safety Population)

Subject Number	Study Period	Was The Subject Randomized?	Date	Randomization Sequence
X	Day -1	XXX	DDMMMYYYY	XXXX-XXXX-XXXX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.2.4 Product Use (Safety Population)

Subject Number	Study Day	Was Product Dispensed?	If No, Reason for Not Done	Was Used Product Collected?	If No, Reason for Not Done	Abstain?*	Product Dispensed	P4M3 ID	Date	Batch Number	Start Time	End Time
X	1	XXX		XXX		XXX	XXX	XXXX	DDMMMYYYY	XXXXXXXX	HH:MM:SS	HH:MM:SS

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
* Did subject abstain from any nicotine/tobacco containing products at least 12 hours prior to product use?
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.2.5 Product Use - Cartridge Weight and Amount of Nicotine Delivered (Safety Population)

Subject Number	Dispense Date	Product Dispensed	P4M3 ID	Pre-product Use Cartridge Weight (mg)	Post-product Use Cartridge Weight (mg)	Difference (mg)	Amount of Nicotine Delivered (mg)
X	DDMMMYYYY	X	XXX	XXXX	XXXX	XXXX	XXXX

CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
The amount of nicotine delivery from P4M3 Gen 2.0 is calculated by dividing the difference in the cartridge weight [mg] by the specific density of the e-liquid [1129.2 mg/mL] multiplied by the nicotine concentration [39.5 mg/mL].
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.2.6 will have the following format:

Listing 15.3.2.6 Subject Using Study Product Status and Study Disposition (Safety Population)

Subject Number	Sequence	Product Administered/Completed			Study Completion	
		CA35	CM35	Cigarettes	Status	Date
X	X	Yes	Yes	Yes	Terminated Study Prematurely	DDMMMYYYY
X	X	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	X	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	X	Yes	Yes	Yes	Completed Study	DDMMMYYYY
		XX	XX	XX		

Sequence 1: < >
Sequence 2: < >
Sequence 3: < >
Sequence 4: < >
Sequence 5: < >
Sequence 6: < >
CA35 = P4M3 Gen 2.0 Classic Auburn
CM35 = P4M3 Gen 2.0 Classic Menthol
Program: /CAXXXXX/sas_prg/stsas/tab cdash_tbldisp2.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listings 15.3.3.1.1 through 15.3.3.1.6 will have the following format:

Page 1 of X

Listing 15.3.3.1.1 Listing of Individual Observed Plasma Nicotine Concentrations Versus Time of P4M3 Gen 2.0 CA35 (PK Population)

Subject Number	Product Sequence	Study Period	Blood Sample Times (minutes) From Start of Product Use: Pre-use	XX	XX	XX	XX	XX	XX	XX
XX	XXX	X	XX	XX	XX	XX	XX	XX	XX	XX
XX	XXX	X	XX	XX	XX	XX	XX	XX	XX	XX
XX	XXX	X	XX	XX	XX	XX	XX	XX	XX	XX

For the calculation of summary statistics, values that are below the limit of quantification (BLQ) of <XX> are treated as… (see footnote)
. = Value missing or not reportable.
Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Notes for Generating the Actual Tables:

- Please use CPConc1 template
- Sample times can be found in Section 6.1.
- No descriptive statistics are to be presented
- 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>.
- Concentrations will be presented to the same precision as in the bioanalytical data.

Listings 15.3.3.1.7 through 15.3.3.1.9 will have the following format:

Page 1 of X

Listing 15.3.3.1.7 Individual Background-Corrected Plasma Nicotine PK Parameters of P4M3 Gen 2.0 (PK Population)

			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

Program: /CAXXXXX/sas_prg/pksas/PROGRAMNAME.SAS DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Notes for Generating the Actual Tables:

- Please use the CPPar1 template, but remove descriptive statistics as these are listings only.
- Footnote to include under the table, as appropriate: <. = Parameter value missing or not calculable>
- PK parameters to be presented are listed in Section 6.3. All concentration parameters will be presented in ng/mL, the AUC parameters in ng*hr/mL, and the time parameters in min.
- Individual exposure-based PK parameters will be reported with 3 significant digits.
- Individual time-based PK parameters will be reported with 2 decimals.

Listing 15.3.3.1.10 will have the following format:

Page 1 of X

Listing 15.3.3.1.10 Individual λz-related Plasma Nicotine PK Parameters of P4M3 Gen 2.0 and Cigarettes (Day 2) (PK Population)

Subject	CA 35					CM35					Cigarettes				
Number	Interval	R^2	N	λz	t½z	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	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	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	X.X - XX.X	X.XXX	X	X.XXX	X.XX

R2 = coefficient of determination of the linear regression
N = Number of points used in λ_z calculation
CA35 = <>
CM35 = <>
. = Parameter value missing or not calculable
Program: /CAXXXXX/sas_prg/pksas PROGRAMNAME.SAS DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Notes for Generating the Actual Tables:

- Please use the CPKel1 template.
- Add column in for 'Product Sequence' and 'Study Day
- 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

Listing 15.3.4.1.1 Pharmacokinetics Blood Sampling (Safety Population)

Subject Number	Study Period	Study Product	Was Blood Sample Collected?	Reason for Not Done	Scheduled Timepoint	Not Done?	Collection Date	Collection Time	Reason for Not Done
X	XXXXXX	XXXXXX	XXX		XXXXXXXXXX		DDMMMYYYY	HH:MM:SS	

CA35 = < >
CM35 = < >
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.2.1 Adverse Events (Safety Population)

Subject Number	Age/ Sex	Study Product	UE?^	System Organ Class/ Preferred Term (Verbatim)	Time From Last Use (DD:HH:MM)	Date:Time Start/ Stop Duration (DD:HH:MM)	Severity/ Serious/ Outcome	Study Product Relationship/ Expectedness	Action / Other Action/ Specify
X	XX/X	XXXX	Yes	XXXXXXXXXXXXX XXXXXXXXXXXXX XXXXXXXXXXXX	XX:XX:XX	DDMMMYYYY HH:MM/ DDMMMYYYY HH:MM/ XX:XX:XX	XXXX No/ XXXXX	XXXXXXXXX/ XXXXXXXX	XXXXXX/ XXXXX/ XXXXXXX

CA35 = < .>
CM35 = < .>
^ = Abbreviation for study product use-emergent (UE),
* = Adverse events are coded according to the MedDRA Version 24.0.
F = Female; M = Male
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: For the AE occurred during the Day -1 or after the discharge from the CRU, the values under study product column will show as Day -1 or Safety Follow-up.

Listing 15.3.4.2.2 Details for Serious Adverse Events (Safety Population)

Subject Number	Age/ Sex	Study Product	UE?^	System Organ Class/ Preferred Term (Verbatim)	Date:Time Start/ Stop Duration (DD:HH:MM)	Serious Event?	Congenital Anomaly/ Birth Defect?	Persistent or Significant Disability or Incapacity?	Hospital-ization?	Life-Threat?	Important Medical Event?
X	XX/X	XXXX	Yes	XXXXXXXXXXXXX XXXXXXXXXXXXX XXXXXXXXXXXX	DDMMMYYYY HH:MM/ DDMMMYYYY HH:MM/ XX:XX:XX	Yes	XX	XX	Yes	XX	XX

Persistent or

CA35 = < .>
CM35 = < .>
^ = Abbreviation for study product use-emergent (UE),
* = Adverse events are coded according to the MedDRA Version 24.0.
F = Female; M = Male
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.2.3 Product Malfunctions, Misuses and Subject Complaints (Safety Population)

Subject Number	Study Period	Study Product	Was There an Event With the P4M3 Gen 2.0?	Date of Event	Time of Event	Severity of Event	Type of Event	If Other, Specify
1	XXXX	XXXX	XXX	DDMMMYYYY	HH:MM	XXX	XXXX	

CA35 = < .>
CM35 = < .>
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.2.4 MDEDR Malfunction (Safety Population)

Subject Number	Study Period	Study Product	Was There an Event With the MDEDR?	Date of Event	Time of Event	MDEDR ID	Type of Event	If Other, Specify	Replacement		
									Date	Time	New ID
1	XXXX	XXXX	XXX	DDMMMYYYY	HH:MM	XXX	XXX		DDMMMYYYY	HH:MM	XXXXX

CA35 = < .>
CM35 = < .>
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listings 15.3.4.3.3, and 15.3.4.3.5 will have the following format.

Listing 15.3.4.3.1 Clinical Laboratory Report - Clinical Chemistry (Safety Population)

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

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
Fast? = Did the subject fast at least 10 hours?
Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

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). Fast? column will only be presented for serum chemistry.

Listing 15.3.4.3.4 and 15.3.4.3.6 will have the following format:

Listing 15.3.4.3.2 Out-of-Range Values and Recheck Results - Clinical chemistry (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Date	Time	Fast?	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)	Parameter5 <Range> (Unit)
X	XX/X	Screen	.	. DDMMMYYYY	HH:MM:SS	XX	XX HN			XX HN	
		1	X	DDMMMYYYY	HH:MM:SS	XXX		XX LNG1	XX LN		XX LYG2

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, G2 = Moderate
Fast? = Did the subject fast at least 10 hours?
Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

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 Listing 15.3.4.3.4 and 15.3.4.3.6 will resemble 15.3.4.3.2. Fast? column will only be presented for serum chemistry.

Programmer Notes: Clinically significant lab values generally will be captured as AEs. 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.

Listing 15.3.4.3.7 will have the following format:

Listing 15.3.4.3.7 Clinically Significant Values and Recheck Results (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Date	Time	Department	Test	Result	Normal Range	Unit
X	XX/X	1	X	DDMMMYYYY	HH:MM:SS	XXXXXXXXXXXXXXX	XXXXXXXXXX	XXX HY	X – X	mg/dL
			X	DDMMMYYYY	HH:MM:SS	XXXXXXXXXXXXXXX	XXXXXXXXXX	XXX	X – X	mg/dL

F = Female, M = Male
H = Above normal range
PI Interpretation: Y = Clinically significant
Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

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.”

Listing 15.3.4.3.8 Alcohol Screen (Safety Population)

Subject Number	Study Period	Was Alcohol Screen Performed?	If No, Reason for Not Done	Date of Test	Category	Result
X	XXXX	XXX		DDMMMYYYY	XXXXXXX	XXXX

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.3.9 Drug Screen (Safety Population)

Subject Number	Study Period	Was a Sample Collected?	If No, Reason for Not Done	Date of Collection	Test Name	Result
X	XXXX	XXX		DDMMMYYYY	XXXXXXX	XXXX

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.3.10 Urine Cotinine Screen (Safety Population)

Subject Number	Study Period	Was the Sample Collected?	If No, Reason for Not Done	Date of Collection	Result (ng/mL)
X	XXXX	XXX		DDMMMYYYY	XXXX

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.3.11 Serology (HIV, HBsAg, HCV) (Safety Population)

Subject Number	Study Period	Was the Sample Collected?	If No, Reason for Not Done	Date of Collection
X	XXXX	XXX		DDMMMYYYY

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.3.12 Pregnancy (Safety Population)

Subject Number	Study Period	Was the Pregnancy Test performed?	If No, Reason for Not Done	Date of Collection	Category	Result
X	XXXX	XXX		DDMMMYYYY	XXXXXX	XXXXXX

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.3.13 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 Status: DRAFT (Page X of Y)

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

Listing 15.3.4.4.1 Vital Signs (I of II) (Safety Population)

Subject Number	Study Day	Were Vital Signs Measured?	If No, Reason for Not Done	Study Product	Date	Time	Time Point	SUP5?	Abstain?	Are Vital Signs Normal, Abnormal?	Specify if Clinically Significant
X	Screening	XXX			DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXXX	
	Day -1	XXX			DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXXX	
	Day 1	XXX		XX	DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXXX	
	Day 2	XXX		XX	DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXXX	

CA35 = < >
CM35 = < >
SUP5 = Subject rested for at least 5 minutes in supine position ?,
Abstain = Subject abstained from products containing nicotine/tobacco for at least 15 minutes?
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.4.2 Vital Signs (II of II) (Safety Population)

Subject Number	Study Day	Were Vital Signs Measured?	Study Product	Date	Time	Time Point	SUP5?	Abstained 15min?	Blood Pressure (mmHg) Systolic / Diastolic	Pulse (bpm)	Respiration (rpm)
X	Screening	XXX		DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXX N / XX N	XX N	XX N
	Day -1	XXX		DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXX ANCS / XX ANCS	XX N	XX N
	Day 1	XXX	XX	DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXX ACS / XX N	XX N	XX N
	Day 2	XXX	XX	DDMMMYYYY	HH:MM	XXXX	XXX	XXX	XXX N / XX ANCS	XX N	XX N

CA35 = < >
CM35 = < >
N = Normal; ANCS = abnormal, not clinically significant; ACS = Abnormal, clinically significant
SUP5? = Subject rested for at least 5 minutes in supine position?
Abstained 15min? = Subject abstained from products containing nicotine/tobacco for at least 15 minutes?
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.5.1 12-Lead Electrocardiogram (I of II) (Safety Population)

Subject Number	Study Day	Was the ECG Performed?	If No, Reason for Not Done	Date	Time	SUP10?	Is the ECG Normal, Abnormal?	Specify if Clinically Significant
X	Screening	XXX		DDMMMYYYY	HH:MM	XXX	XXXX	
	Day -1	XXX		DDMMMYYYY	HH:MM	XXX	XXXX	
	Day 3	XXX		DDMMMYYYY	HH:MM	XXX	XXXX	

SUP10 = Subject rested for at least 10 minutes in supine position?
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.5.2 12-Lead Electrocardiogram (II of II) (Safety Population)

Subject Number	Study Day	Was the ECG Performed?	Date	Time	Heart Rate (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTcF* (msec)
X	Screening	XXX	DDMMMYYYY	HH:MM	XX	XXX.X	XX.X	XXX.X	XXX.X
	Day -1	XXX	DDMMMYYYY	HH:MM	XX	XXX.X	XX.X	XXX.X	XXX.X

Note: QTcF* = QTc corrected using Fridericia's correction.
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.6.1 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?	Due to AE?
X	XXXXX		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 01MAR2021..
Freq. = Frequency
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.4.7.1 Spirometry (Safety Population)

Subject Number	Study Period	Was the Spirometry Performed?	ND?	Date	Time	15?/ 1h?	Is the Result Normal, Abnormal?	Specify If CS	FEV1 (L)	FEV1 %Predicted	FVC (L)	FVC %Preficted	FEV1/FVC (%)	FEV1/FVC %Predicted
X	Screening	YES		DMMMYYYY	HH:MM	Y/Y	XX		XX	XX	XX	XX	XXX	XX

ND? = If No, reason for not done, CS = Clinically significant
15? = Subject rested for at least 15 minutes in sitting position?
1h? = Subject did not use cigarettes for at least 1 hour?
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y).

Listing 15.3.4.8.1 CYP2A6 Activity (Trans-3'-Hydroxycotinine and Cotinine) (Safety Population)

Subject Number	Study Day	Visit Date	Trans-3-Hydroxycotinine (ng/mL)	Cotinine (ng/mL)	Ratio
X	Screening	DDMMMYYYY	XXX.XX	XXX.XX	X.XXX

Note: Ratio = Trans-3'-Hydroxycotinine/Cotinine
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.5.1.1 Original Responses of ABOUT - Product Experience Questionnaire (PK Population)

Subject Number	Study Day	Was the Questionnaire Completed?	If No, Reason for Not Done	Study Product	Date	Time	Question* 1	2	3	4	5	6	7	8	9	10	11	12
X	X	XXX		XXXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	X	X	X	X
	X	XXX		XXXXXXX	DDMMMYYYY	HH:MM	X	X	X	X	X	X	X	X	X	X	X	X

CA35 = < >
CM35 = < >
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?
11a. Did it immediately relieve your craving for a cigarette? 11b. Did it immediately relieve your craving for P4M3 Gen 2.0? 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 Status: DRAFT (Page X of Y)

Listing 15.3.5.1.2 Subscales of ABOUT - Product Experience Questionnaire (PK Population)

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

CA35 = < >
CM35 = < >
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 Status: DRAFT (Page X of Y)

Listing 15.3.5.1.3 VAS Craving Assessment (PK Population)

Subject Number	Study Day	Was the VAS Craving Assessment Performed?	If No, Reason for Not Done	Study Product	Date	Scheduled TimePoint	Time	VAS Score	Not Done	Reason for Not Done
X	X	XXX		XXXX	DDMMMYYYY	XXXXXXXX	HH:MM	XXX		

CA35 = < >
CM35 = < >
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.5.1.4 VAS Liking Assessment (PK Population)

Subject Number	Study Day	Was the VAS Liking Assessment Performed?	If No, Reason for Not Done	Study Product	Date	Scheduled TimePoint	Time	VAS Score	Not Done	Reason for Not Done
X	X	XXX		XXXX	DDMMMYYYY	XXXXXXXX	HH:MM	XXX		

CA35 = < >
CM35 = < >
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.5.2.1 Human Puffing Topography Collection (PK Population)

Subject Number	Study Period	Was HPT Completed?	If No, Reason for Not Done	Study Product	Date	MDEDR ID	Start Time	End Time
X	X	XXX		XXXXX	DDMMMYYYY	XXXX	HH:MM:SS	HH:MM:SS

CA35 = < >
CM35 = < >
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Listing 15.3.5.2.2 Human Puffing Topography Parameters (Per Puff) (PK Population)

Subject Number	Study Period	Study Product	Parameter1 (unit1)	Parameter 2 (unit2)	Parameter 3 (unit3)	etc.
X	X	XXXXX	XXXX	XXXXX	XXXXX	

CA35 = < >
CM35 = < >
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: Replace Parameter1 and unit1 etc. with the real parameter name and unit. If all the parameters cannot be fit on one page, the listing will be separated as two parts as Listing 15.3.4.2.1 (I of II) and 15.3.4.2.1 (II of II).

Listing 15.3.5.2.3 Human Puffing Topography Parameters (Per Product experience) (PK Population)

Subject Number	Study Period	Study Product	Parameter1 (unit1)	Parameter 2 (unit2)	Parameter 3 (unit3)	etc.
X	X	XXXXX	XXXX	XXXXX	XXXXX	

CA35 = < >
CM35 = < >
Program: /CAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM Status: DRAFT (Page X of Y)

Programmer note: Replace Parameter1 and unit1 etc. with the real parameter name and unit. If all the parameters cannot be fit on one page, the listing will be separated as two parts as Listing 15.3. 5.2.3 (I of II) and 15.3.5.2.3 (II of II).