PHILIP MORRIS PRODUCTS S.A.

Statistical Analysis Plan

Study Number:	P4-REXC-06
Study Title:	A randomized, controlled, open-label, 4-arm parallel group study to demonstrate reductions in exposure to selected harmful and potentially harmful constituents (HPHC) in healthy smokers switching to 2 variants of P4M3 Gen 2.0, an Electronic Nicotine Delivery System (ENDS), compared to continuing smoking cigarettes, or abstaining from smoking, for 5 days in a confinement setting
Product Name:	P4M3 Gen 2.0
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	2.0, Approved
Date:	26 Aug 2022

STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

When this page is signed the Statistical Analysis Plan (SAP) is considered final. The signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs).

CRO Approval:

[redacted]	Refer to electronic signature
Statistician II	
[redacted]	

Sponsor Approval:

[redacted]	Refer to electronic signature
Sr Scientist - Biostatistics	
Philip Morris Products S.A.	

[redacted]	Refer to electronic signature
Sr Scientist - Biostatistics	
Philip Morris Products S.A.	

[redacted]	Refer to electronic signature
Sr Clinical Scientist	
Philip Morris Products S.A.	

[redacted]	Refer to electronic signature
Manager Medical Safety Operations	
Philip Morris Products S.A.	

[redacted]	Refer to electronic signature
Head of Biostatistics	
Philip Morris Products S.A.	

TABLE OF CONTENTS

1 ABBREVIATIONS OF TERMS

2-CyEMA	2-cyanoethyl mercapturic acid
3-OH-B[a]P	Total 3-hydroxybenzo(a)pyrene
3-HMPMA	3-hydroxy-1-methylpropylmercapturic acid
3-HPMA	3-hydroxypropyl mercapturic acid
AE	Adverse event
ATC	Anatomical Therapeutic and Chemical
BMI	Body mass index
BoExp	Biomarker of exposure
BoPH	Biomarker of potential harm
CA35	Classic Auburn 3.5% nicotine
CM35	Classic Menthol 3.5% nicotine
CAF	Caffeine
CI	Confidence interval
CIG	Cigarette
COHb	Carboxyhemoglobin
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CV (statistics)	Coefficient of variation
DHPMA	2,3-dihydroxypropylmercapturic acid
ECG	Electrocardiogram
ENDS	Electronic Nicotine Delivery System
EOS	End of study
FAS	Full analysis set
FDA	Federal Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström Tobacco and Nicotine Dependence
FVC	Forced vital capacity
GCV (statistics)	Geometric coefficient of variation
GMR	Geometric mean ratio

H	Hypothesis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency viruses
HPHC	Harmful and potentially harmful constituents
HPT	Human Puffing Topography
ICF	Informed consent form
IEC	International ethic committee
ITT	Intention to treat
IxRS	Interactive web and voice response system
LLOQ	Lower limit of quantification
LS	Least squares
LSMEANS	Least squares means
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model for repeated measures
NCT	ClinicalTrial.gov identification number
NEQ	Nicotine Equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
P4M3	Combined CA35 and CM35 arms
PMI	Philip Morris International
PMP	Philip Morris Products SA
PPS	Per protocol set
PT	Preferred term
PX	Paraxanthine
QC	Quality control
RRP	Reduced risk product
S-PMA	*S*-phenylmercapturic acid
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class

TFL	Tables, figures, and listings
THS	Tobacco Heating System
TNP	Tobacco and/or nicotine containing product
ULOQ	Upper limit of quantification
WHO	World Health Organization

2 INTRODUCTION

This statistical analysis plan (SAP) has been developed to supplement the statistical analyses described in the clinical study protocol (final version 4.0) dated 13 Apr 2022.

The SAP contains a complete and detailed specification of the statistical analyses. A detailed description of the planned Tables, Figures and Listings (TFLs) will be provided in a separate TFLs shell document. Any changes to the TFL shell numbering or to the title/footnote 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:

- Good Clinical Practice (GCP) guidelines E6 (R1)
- International Council on Harmonization (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".
- ICH E9 (R1) addendum on “Estimands and sensitivity analysis in clinical trials”.
- Clinical Study Protocol final version 4.0 dated 13 April 2022.

2.1 Revision History

Version	Date of Revision	Revision
1.0	Refer to electronic signature date	Initial Version
2.0	Refer to electronic signature date	Correction and clarification of the formula used to determine nicotine equivalents (5.1.1)

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

The primary objective of this study is:

1. To demonstrate the reduction of biomarkers of exposure (BoExp) listed in Table 1 to selected harmful and potentially harmful constituents (HPHC) in smokers switching from

cigarette (CIG) to P4M3 (combined CA35 and CM35 arms) compared to continuing cigarette smoking for 5 days.

Table 1 List of BoExp used in the primary objective

BoExp	HPHC	Matrix
3-hydroxypropyl mercapturic acid (3-HPMA)	Acrolein	Urine[1]
2-cyanoethyl mercapturic acid (2-CyEMA)	Acrylonitrile	Urine[1]
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	Urine[1]
Carboxyhemoglobin (COHb)	Carbon monoxide (CO)	Blood[2]

[1]*BoExp in urine will be expressed as concentration adjusted for creatinine in 24-hour urine*
[2]*BoExp in blood expressed as % of saturation of hemoglobin.*

The main assessment of the primary objective will be done in subjects who are adherent to their randomized arms (who belong to the Per Protocol Set, see section 8.3).

3.2 Secondary Objectives

3.2.1 Key Secondary Objectives and Endpoints

The key secondary objectives of this study are:

1. To demonstrate the reduction of BoExp given in Table 2 to selected HPHC in smokers switching from CIG to P4M3 (combined CA35 and CM35 arms) compared to continuing CIG smoking for 5 days.

Table 2 List of BoExp used in the key secondary objective

BoExp	HPHC	Matrix
S-phenylmercapturic acid (S-PMA)	Benzene	Urine[1]
3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA)	Crotonaldehyde	Urine[1]
Total N-nitrosonornicotine (total NNN)	N-nitrosonornicotine	Urine[1]

Total 3-hydroxybenzo(a)pyrene (3-OH-B[a]P)	Benzo(a)pyrene	Urine[1]

[1]*BoExp in urine will be expressed as concentration adjusted for creatinine in 24-hour urine*

2. To demonstrate the reduction of BoExp to selected HPHC given in Table 1 in smokers switching from CIG to P4M3 CA35 only compared to continuing CIG smoking for 5 days.
3. To demonstrate the reduction of BoExp to selected HPHC given in Table 2 in smokers switching from CIG to P4M3 CA35 only compared to continuing CIG smoking for 5 days.
4. To demonstrate the reduction of BoExp to selected HPHC given in Table 1 in smokers switching from CIG to P4M3 CM35 only compared to continuing CIG smoking for 5 days.
5. To demonstrate the reduction of BoExp to selected HPHC given in Table 2 in smokers switching from CIG to P4M3 CM35 only compared to continuing CIG smoking for 5 days.

The main assessment of the key secondary objectives will be done in subjects who are adherent to their randomized arms (who belong to the Per Protocol Set, see section 8.3).

These key secondary objectives will only be evaluated if the primary objective is successfully demonstrated. They will be assessed sequentially, and the fixed sequence of testing will stop if any of the primary or key secondary objectives are not demonstrated (see Figure 2, section 9.6.3.1).

3.2.2 Secondary Objective and Endpoints

1. The secondary objective of this study is to monitor safety and tolerability in all subjects during the study.

   Endpoints

   - Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs),
   - Incidence and frequency of P4M3 product events including malfunction/misuse,
   - Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, QTcF intervals),
   - Vital signs changes from baseline (systolic and diastolic blood pressure, heart rate and respiratory rate),
   - Spirometry changes from baseline (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEV_1/FVC),
   - Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel,
   - Concomitant medications.

3.3 Exploratory Objectives and Endpoints

The exploratory objectives of this study are:

1. The exploratory objective 1 of this study is to determine the levels of BoExp to selected HPHC given in Table 3 in smokers switching from CIG to P4M3 (CA35 and CM35 arms combined and separately) compared to continuing CIG smoking for 5 days.

Table 3 List of BoExp used as exploratory objective

BoExp	HPHC	Matrix
2-hydroxypropylmercapturic acid (2-HPMA)	Propylene oxide	Urine[1]
2,3-dihydroxypropylmercapturic acid (DHPMA)	Glycidol	Urine[1]
Nicotine equivalents (NEQ[2])	Nicotine	Urine[1]

[1]*BoExp in urine expressed as concentration adjusted for creatinine in 24-hour urine;*

[2]*NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'hydroxy-cotinine-glucuronide.*

2. The exploratory objective 2 of this study is to determine the reductions of BoExp to selected HPHC given in Table 1, Table 2, and Table 3 in smokers quitting smoking compared to continuing CIG smoking or switching from CIG to P4M3 (CA35 and CM35 arms combined and separately) for 5 days.
3. The exploratory objective 3 of this study is to describe the nicotine/tobacco product use in smokers switching from CIG to P4M3 (CA35 and CM35 arms combined and separately) compared to continuing CIG smoking.

   Endpoints (Day -1 to Day 5)

   - Daily number of CIG (Day -1 all subjects, Day 1 to 5 subjects of CIG arm only),
   - Daily number of P4M3 Cartridges (Day 1 to 5 subjects of P4M3 arms only),
   - Daily e-liquid used determined by weight difference of the Cartridge(s) before and after daily use.
4. The exploratory objective 4 of this study is to describe reinforcing effects related to tobacco/nicotine containing products use in smokers switching from CIG smoking to P4M3 (CA35 and CM35 arms combined and separately) compared to continued CIG smoking.

   Endpoints (Day -1 to Day 5)

- Subscale scores of Product Experience (ABOUT – Product Experience) questionnaire (assessed only in subjects randomized to P4M3 or CIG).

5. The exploratory objective 5 of this study is to describe the Human Puffing Topography (HPT) over the entire exposure period in subjects switching to P4M3 (CA35 or CM35 arms combined and separately).

   Endpoints (Day 1 to Day 5)

   - Puffing topography parameters as per-product use experience and per-day parameters (Table 4 and Table 5):

Table 4 Per-Puff Parameters

Description	Variable	Unit
Puff ID	Ni	
Puff Volume	Vi	mL
Puff duration	Di	s
Average puff low	Qmi	mL/s
Peak flow	Qci	mL/s
Inter puff interval	Ii	s
Sum of Ii and Di	DFi	s
Peak flow position	PosQci	%
Power setting	Powi	W

Table 5 Per-Day Parameters

Parameter	Variable	Formula	Unit
Total number of puffs/day	NPC	Count Ni	
Total puff volume	TVOL	∑ Vi	mL
Total puff duration/day	TDi	∑ Di	s
Average puff volume	AvgVi	∑ Vi / NPC, i=1 ... NPC	mL
Average puff duration	AvgDi	∑ Di / NPC, i=1 ... NPC	s
Average flow	AvgQmi	∑ Qmi / NPC, i=1 … NPC	mL/s

Average Peak flow	AvgQci	∑ Qci / NPC, i=1 … NPC	mL/s
Average inter puff interval	AvgIi	∑ Ii / NPC, i=1 … NPC	s
Total puffing duration (total product use duration, session length)	TDFi	∑ DFi	s
Puff Frequency	PFreq	NPC/(TDFi/60)	
% of puffs with higher power setting	PctPuffsHighPow	100*Count Ni at high power/NPC	%

6. The exploratory objective 6 of this study is to evaluate the cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching to P4M3 (CA35 and CM35 arms combined and separately) and smoking abstinence compared to continued CIG smoking.

   Endpoint (Day -1, Day 5)

   - Molar metabolic ratio of paraxanthine/caffeine in plasma.

3.4 Additional Endpoints

The following assessments will be performed as part of the screening procedures or to collect characteristics of the study subjects:

- Demographics (sex, age, race, body height, body weight, BMI)
- Medical History, Concomitant Disease, Previous and Concomitant Medications
- Tests for pregnancy
- Tests for drugs, cotinine, and alcohol
- Physical examination
- Vital signs
- Spirometry
- Electrocardiogram (ECG)
- Clinical chemistry, hematology, and urine analysis
- Serology
- CYP1A2 activity
- Creatinine in 24-h urine

- Questions on tobacco/nicotine-containing products use history
- Fagerström Test for Nicotine Dependence (Revised Version)
- ABOUT – Product Experience Questionnaire

3.5 Study Hypotheses and Evaluation Criteria

3.5.1 Hypotheses

The primary study hypothesis is that there is a reduction in all BoExp to the selected HPHC that are examined for the primary objective, in subjects switching to P4M3 (subjects of CA35 and CM35 pooled together) compared to subjects continuing CIG.

Specifically, the primary hypothesis (H_1) is:

- The geometric mean ratio (P4M3/CIG) of 3-HPMA at Day 5 is less than 1
  and
- The geometric mean ratio (P4M3/CIG) of 2-CyEMA at Day 5 is less than 1
  and
- The geometric mean ratio (P4M3/CIG) of total NNAL at Day 5 is less than 1
  and
- The geometric mean ratio (P4M3/CIG) of COHb at Day 5 is less than 1

For the key secondary objective, the hypotheses (H_x) are defined sequentially in this order:
H_2:

- The geometric mean ratio (P4M3/CIG) of S-PMA at Day 5 is less than 1
  and
- The geometric mean ratio (P4M3/CIG) of 3-HMPMA at Day 5 is less than 1
  and
- The geometric mean ratio (P4M3/CIG) of total NNN at Day 5 is less than 1
  and
- The geometric mean ratio (P4M3/CIG) of 3-OH-B[a]P at Day 5 is less than 1

H_3:

- The geometric mean ratio (CA35/CIG) of 3-HPMA at Day 5 is less than 1
  and

- The geometric mean ratio (CA35/CIG) of 2-CyEMA at Day 5 is less than 1
  and
- The geometric mean ratio (CA35/CIG) of total NNAL at Day 5 is less than 1
  and
- The geometric mean ratio (CA35/CIG) of COHb at Day 5 is less than 1

H_4:

- The geometric mean ratio (CA35/CIG) of S-PMA at Day 5 is less than 1
  and
- The geometric mean ratio (CA35/CIG) of 3-HMPMA at Day 5 is less than 1
  and
- The geometric mean ratio (CA35/CIG) of total NNN at Day 5 is less than 1
  and
- The geometric mean ratio (CA35/CIG) of 3-OH-B[a]P at Day 5 is less than 1

H_5:

- The geometric mean ratio (CM35/CIG) of 3-HPMA at Day 5 is less than 1
  and
- The geometric mean ratio (CM35/CIG) of 2-CyEMA at Day 5 is less than 1
  and
- The geometric mean ratio (CM35/CIG) of total NNAL at Day 5 is less than 1
  and
- The geometric mean ratio (CM35/CIG) of COHb at Day 5 is less than 1

H_6:

- The geometric mean ratio (CM35/CIG) of S-PMA at Day 5 is less than 1
  and
- The geometric mean ratio (CM35/CIG) of 3-HMPMA at Day 5 is less than 1
  and
- The geometric mean ratio (CM35/CIG) of total NNN at Day 5 is less than 1
  and
- The geometric mean ratio (CM35/CIG) of 3-OH-B[a]P at Day 5 is less than 1

3.5.2 Evaluation Criteria

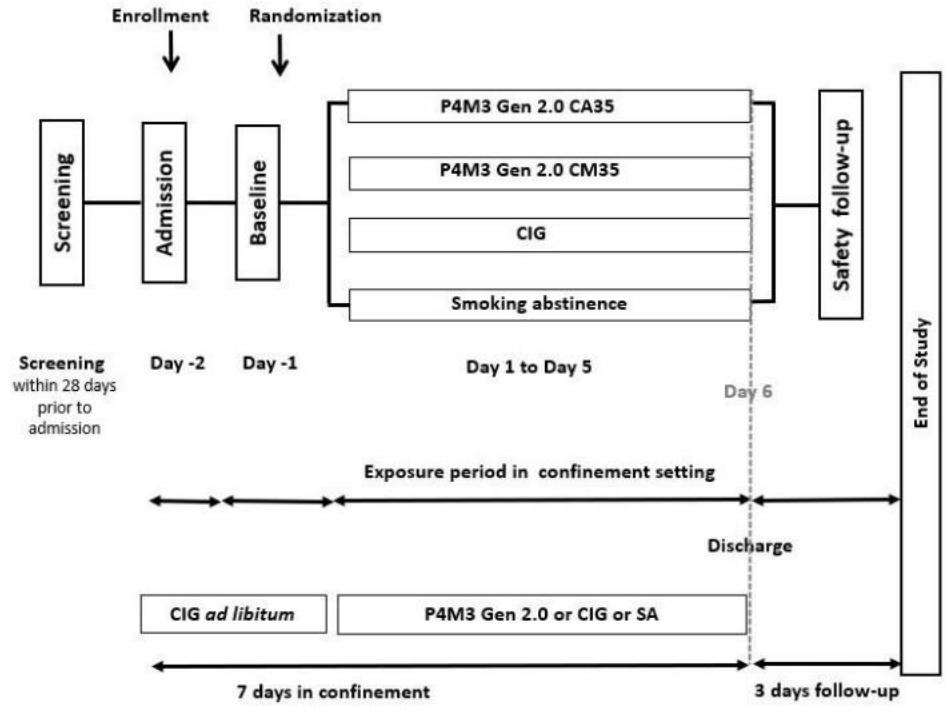
The study will be declared successful if a reduction is demonstrated on all endpoints tested to support the co-primary objectives (3-HPMA, 2-CyEMA, total NNAL, and COHb), using a one-sided test-wise type I error level of 2.5%.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, controlled, open-label, 4-arm parallel study with a stratified randomization by sex. Quotas will be applied to ensure that the randomized subjects contain at least 40% of both sexes (males and females) per arm.

This is an *ad libitum* smoking/vaping study with unrestricted product use (P4M3 or CIG, in the respective arms) for 5 days exposure period in confinement followed by a 3-day Safety follow-up period (Figure 1).



Abbreviations:
CA35 = P4M3 Classic Auburn 3.5% nicotine; CM35 = P4M3 Classic Menthol 3.5% nicotine; CIG = Cigarette; SA = Smoking abstinence

Figure 1 Study Design

- Screening period (from Day -30 until Day -3):

  The screening period covers up to four weeks prior to admission. A presentation of P4M3 (without product use) will be done by the site staff during the Screening visit. All subjects will receive information on the risks of smoking and smoking cessation advice. Eligible subjects will return to the investigational site for verification of eligibility.

- Admission (from Day -2 until morning of Day -1):

  On Day -2 (admission), after all inclusion/exclusion criteria are checked, all eligible subjects will be enrolled and perform a product test using both P4M3 variants: tobacco flavor "Classic Auburn" 3.5% nicotine (CA35) and menthol flavor "Classic Menthol" 3.5% nicotine (CM35), with an *ad libitum* use regimen for a duration of approximately 10 minutes *ad libitum* use per flavor. After the product test, subjects not willing to use P4M3 during the study will be discontinued and will be replaced. Subjects willing to continue participation will start their confinement period. CIG smoking will be allowed *ad libitum* from the time of admission of the subject until approximately 11:00 PM, except before/during assessments requiring smoking breaks. Use of any TNP other than CIG (and P4M3 for the product test) will not be allowed after admission.

  Provided that the 28-day Screening period is not exceeded, alternate subjects (not yet randomized) have to repeat the admission visit of the following group to re-confirm their eligibility for randomization.

- Baseline (from Day -1, 06:30 AM until Day 1, 06:29 AM):

  Subjects may continue smoking their CIG *ad libitum,* except before/during assessments requiring smoking breaks. The 24-hour urine collection for Day -1 will start in the morning of Day -1 (urine collection details provided in Appendix A of the protocol). Baseline assessments will be performed as indicated in Appendix A of the protocol.

  On Day -1, subjects will be randomized. Subjects will be informed about their randomized study arm by the study site staff on Day 1 prior to start of product use. The four randomization arms are:

  - P4M3 CA35 arm: 18 subjects, *ad libitum* use of P4M3 using CA Cartridges
  - P4M3 CM35 arm: 18 subjects, *ad libitum* use of P4M3 using CM Cartridges
  - CIG arm: 18 subjects, *ad libitum* use of their own preferred CIG brand
  - SA arm: 18 subjects who will abstain from CIG smoking

- Exposure period in confinement setting (from Day 1 until Day 5 11:00 PM, followed by Discharge at Day 6):

  The exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product in the P4M3 and CIG arms. Use of any TNP other than the assigned product will not be allowed and may, at the discretion of the investigator, result in the subject's discontinuation from the study. Subjects allocated to the SA arm will be asked to abstain from CIG smoking.

  Daily 24-hour urine will be collected from Day 1 to Day 5. On Day 1, product use must not start before the end of 24-hour urine collection of Day -1. The 24-hour urine collection period for Day 5 will end in the morning of Day 6 prior to Discharge.

  During the confinement period, site staff will distribute assigned products to the subjects and record all products distributed in the source documentation.

  Any subject who wants to attempt to quit using tobacco or nicotine containing products at any time during the study (i.e., P4M3, CIG) will be encouraged to do so and will be referred to appropriate medical services. This will not affect subject's financial compensation, and the subject will remain in the study.

- Safety follow-up period (from Discharge at Day 6 until the end of the Safety follow-up period):

  After Discharge at Day 6 or from the day of early termination, subjects will enter a 3-day Safety follow-up period during which AEs/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.

4.2 Rationale For Study Design

This clinical study aims to demonstrate the reduction of BoExp to selected HPHC in smokers switching from CIG to P4M3, a candidate RRP[1], as compared smokers continuing smoking CIG, or to smoking abstinence (SA). A reduction of exposure to HPHC derived from CIG smoke is expected to diminish the health risk of nicotine consumption if switching completely to ENDS.

The exposure period in confinement will provide information on exposure reductions achievable in a well-controlled environment with full control on daily P4M3/CIG consumption and compared to SA.

[1] Reduced risk products ("RRPs") is the term used by PMI to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

HPHC considered to be of health concern have been reported by different regulatory bodies and health organizations [1, 2]. Lists of HPHC to be reported in tobacco smoke have consequently been developed, as described, for example in the FDA draft guidance on "Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke" [3]. More recently, a guidance was issued by the FDA on which HPHC to be considered for reporting in e-liquids or aerosols of ENDS [4].

It is not possible to measure each of those potentially toxic constituents in humans, due to constraints in availability of validated, reliable methods, or simply the absence of suitable BoExp. A selection of HPHC to be evaluated in this study was thus performed based on the following criteria:

1. The HPHC selected are representative of a variety of chemical classes and organ toxicity classes as defined by the FDA (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, and addiction potential) [2]
2. The HPHC reflects a specific toxic exposure or is a reliable surrogate of exposure to HPHC
3. The HPHC assessed cover a broad range of formation temperatures
4. The HPHC is specific to smoking with other sources being minor or non-existent
5. The BoExp to a HPHC is reliably detectable using validated, reproducible, precise analytical methods
6. The BoExp to a HPHC has a half-life that is suitable with the schedule of assessments

Other parameters such as product evaluation, and subjective effects related to smoking including smoking urges and withdrawal symptoms, and the intent to use, will be evaluated.

Twenty-four hours urine collection conducted in this study is the standard method to measure the levels of excretion of BoExp.

All subjects in the CIG arm will be asked to buy their own CIG according to their anticipated needs for the study to minimize any changes in their smoking behavior.

4.3 Appropriateness of Measurements

All laboratory measures utilized for this study are validated and are appropriate for the study assessments.

All the self-report measures to be used in this study have been developed following the best practices (including the FDA's Guidance for Industry Patient-Reported Outcome (PRO) Measures [5]), which provide the scientific basis for the development, modification, and

validation of PRO measures in support of clinical and regulatory research. They are validated and previously published or adapted versions of validated questionnaires.

4.4 Study Duration

The entire study duration per subject will be 11 to 38 days. This will include a screening period of up to 28 days prior to Admission (Day -30 to Day -3), followed by a 7-day confinement period (Day -2 to Day 5, and Discharge on Day 6), and a 3-day Safety follow-up period.

The EOS for a randomized subject is defined as the completion of the 3-day Safety follow-up period either after Discharge on Day 6, or after the date of early termination of the subject. The EOS of the entire study is the end of the Safety Follow-up Period for the last subject.

4.4.1 Timing of Confinement Period

The confinement period will begin after enrolment following admission procedures from Day –2, followed by Baseline assessments and randomization during Day -1. The Exposure period in confinement consists of 5 days (Day 1 to Day 5) of *ad libitum* use of the assigned product in the P4M3 and CIG arms.

After Discharge at Day 6 or from the day of early termination, subjects will enter a 3-day Safety follow-up period during which AEs/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.

4.5 Study Population

Approximately 72 smoking healthy female or male subjects who have smoked on average at least 10 regular or menthol CIG per day for the last 4 weeks prior to Admission will be randomized (stratified by sex) into this study. Quotas will be applied to ensure that the randomized subjects contain at least 40% of both sexes (males and females) per arm.

The maximum number of CIG smoked daily is not limited. Subjects must have been smoking for at least 3 years of smoking prior to the Screening Visit. There will be no brand restrictions of CIG. Smoking status will be verified with a urinary cotinine test (cotinine ≥200 ng/mL).

4.5.1 Inclusion Criteria

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

Inclusion Criteria	**Screening**	**Day -2**

1. Subject has signed the ICF and is able to understand the information provided in the ICF.	X	
2. Subject is male or female and between 21 and 65 years old (inclusive).	X	
3. Subject has been a smoker for ≥3 years prior to the screening visit (smoking cessation attempts during this period, if any, did not last >6 months).	X	
4. Subject has continuously smoked on average ≥10 commercially available mentholated or non-mentholated CIGs per day over the last 4 weeks prior to screening and admission. Smoking status will be verified based on a urinary cotinine test (cotinine ≥200 ng/mL).	X	X
5. Subject is healthy as judged by the Investigator based on available assessments from the screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, and medical history).	X	

4.5.2 Exclusion Criteria

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

Exclusion Criteria	**Screening**	**Day -2**
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., in emergency situations, under guardianship, or prisoners).	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), which as per the judgment of the Investigator would jeopardize the safety of the subject.	X	
4. Subject experienced within 30 days prior to screening/admission a body temperature >37.5°C or an acute illness (e.g., upper respiratory-tract infection, viral infection, etc.)	X	X
5. As per the Investigator's judgment, the subject has medical conditions which do or will require a medical intervention (e.g., start of treatment, surgery, hospitalization) during the study participation, which may interfere with the study participation and/or study results.	X	
6. Subject has relevant history of, or current asthma condition or COPD condition, and/or clinically significant spirometry findings at Screening or Baseline	X	
7. Subject has donated blood or received whole blood or blood products within 3 months prior to screening.	X	
8. BMI <18.5 kg/m^2 or ≥32.0 kg/m^2.	X	
9. Positive serology test for HIV 1/2, HBV, or HCV.	X	
10. Subject has a positive alcohol breath test and/or has a history of alcohol abuse which as per judgement of the PI could interfere with their participation in the study.	X	X
11. The subject has a positive urine drug test.	X	X
12. Subject or one of their family members[a] is a current or former employee of the tobacco or e-cigarette 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 1 month or five half-lives of the previous investigational drug/product (whatever the longer) prior to Screening.	X	
15. Subject has been previously screened or enrolled in this study.	X	
16. Subject is pregnant (does not have negative pregnancy tests at screening 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	

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, bilateral oophorectomy, 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.*

4.5.3 Discontinuation of Subjects from the Study

Discontinued subjects (i.e., enrolled subjects that do not complete the study) will include both subjects who withdraw from the study (subject's decision) or subjects who are discontinued from the study by the decision of the Investigator.

Subjects will be informed that they are free to withdraw from the study at any time. Subjects should be questioned for the reason of withdrawal from the study, although they are not obliged to disclose it.

If the subject withdraws from the study, this information will be fully documented by the PI or designee including:

- The early termination procedures for safety assessments will be performed as defined in section 9.5 of the study protocol, unless the subject refuses to perform the assessments.
- The samples collected up to the time of withdrawal that have been analyzed and data collected up to the time of withdrawal will be used in the analysis and report. If the subject refuses that non-analyzed samples and data will be used, he/she needs to document his disagreement in writing.

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

- Withdrawal of informed consent
- Non-adherence to allocated product or to smoking abstinence
- Subject becomes an employee of the investigational site, or any other parties involved in the study, or their first-degree relatives (parent, sibling, and child)
- Any AE or condition (including clinically significant changes in a laboratory parameter) which at the discretion of the Investigator no longer justifies the subject's participation in this study
- Positive pregnancy test
- Discontinuation considered to be in the best interest of the subject or the other subjects, as judged by the Investigator
- Subject unwilling to use the product during the entire study duration after having done the product test.
- An alternate subject that has completed the Screening period and has not been randomized.
- The Sponsor terminates the study, or the study terminates at a particular site. If the Sponsor decides to prematurely terminate the study, the subjects will be promptly informed. The Investigator or designee should report the fact and the reason in writing to the IEC
- The Investigator terminates the study or suspends the trial (e.g., due to a loss of key staff members, change of circumstances). If the Investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator must inform the institution as applicable, and must promptly inform in the sponsor and the IEC in writing, including a detailed explanation.

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

- Non-compliance to the study procedures based on the judgment of the Investigator
- Violation of eligibility criteria

Subjects who will be discontinued from the study before enrolment 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 (except alternate subjects). In general, subjects that are discontinued after randomization will not be replaced. Should there be the need to discontinue all subjects from one cohort, e.g., all subjects suspected to have contracted a disease pathogen, subjects for a replacement cohort may be enrolled and randomized.

4.5.4 Lost to Follow-up

A reasonable attempt will be made to contact all participants needing to complete or resolve post-study activities (e.g., safety laboratory, physical examination, on-going AEs). Two contacts will be made via contact information provided by the subject (e.g., telephone number, cell phone number, email address), allowing 1 day between attempts for response.

The first contact attempt should take place within approximately 1-2 days of the participant's last visit to the investigational site. If contact is not possible, a follow-up letter will be sent to the participant, allowing approximately 5 business days from the time of delivery for a response. A progress note will be added in the data collection system for documentation. After a letter is sent, there should be no additional phone calls unless the participant has attempted to contact the investigational site and a return call attempt is made.

If post-study follow-up has not been resolved within approximately 5 business days following delivery confirmation or the letter is not deliverable, the participant is considered Lost to follow-up. This is documented in the progress note and outstanding AEs are updated. The date of Lost to follow-up corresponds to the date of the end of study of the subject.

The Investigator or designee(s) will declare the subject Lost to follow-up if the investigational site lost contact to the subject and the subject has reached the maximum number of study days (31 days) without making any contact.

4.5.5 Violation of Selection Criteria

Detected violations of eligibility criteria post enrollment may require subjects to be discontinued from the study based on a case-by-case decision of the Investigator.

4.6 Product Allocation and Blinding

4.6.1 Method for Assigning Subjects to Study Arms

At the end of the Baseline period enrolled subjects will be randomized using an interactive web and voice response system (IxRS) on Day -1 at any time during the day. Subjects will be informed of their randomized study arm in the morning of Day 1, prior to 06:30 AM (the start of the exposure period). Subjects will be randomized (stratified by sex) to one of the four study arms (CA35, CM35, CIG, and SA) in a 1:1:1:1 ratio.

Quotas will be applied to ensure that the randomized subjects contain at least 40% of both sexes (males and females) per arm.

Any alternate subject that has not been randomized will enter the 3-day Safety follow-up period.

4.6.2 Blinding

This is an open-label study. Therefore, the subjects and Investigators or designees will be unblinded to the subject's study arm. However, there will be a limited degree of blinding in the data review and data analysis process. The protocol deviations will be classified by a blinded team (blinded to the randomization allocation). PMI and contract research organization (CRO) personnel will be blinded to the randomization groups as summarized below in Table 6.

Table 6 Blinding Scheme

Blinded Study Personnel	Blinded Data[1]	End of Blinding Period
PMI and CRO study statisticians	Blinded to all BoExp data	After the SAP finalization (excluding TFL shells finalization)
PMI clinical scientist	Blinded to all BoExp data	After the SAP finalization (excluding TFL shells finalization)

[1]Blinded data will be made accessible to the blinded personnel by means of a dummy group or masking. As part of the PMI quality control (QC) activity, data listings will be reviewed by the CRO and PMI before database lock, with no access to the arm information. Full details will be available in the data review plan.

4.6.3 Compliance to Product Allocation

During the confinement period, compliance will be ensured by strict distribution and collection of any used and unused P4M3, comprising of the P4M3 Battery Unit and the P4M3 Cartridge, and CIG butts by designated investigational site staff. Distribution and return of these products will be documented in appropriate logs.

5 DERIVED AND COMPUTED VARIABLES

5.1 Biomarkers of Exposure

BoExp measured in urine will be expressed as mass concentration adjusted for creatinine in 24-hour urine:

$$\text{Biomarker (corrected for creatinine)} = \frac{[\text{Biomarker}]}{[\text{Creatinine}]}$$

where the [ ] indicated concentrations measured from the same 24-h urine collection.

5.1.1 Nicotine Equivalents

The quantity excreted of NEQ over 24 hours will be derived according to the formula below. The concentrations reported for free nicotine and its five major metabolites will not be used as analysis variables.

$$\begin{aligned}\text{NEQ [mg/L]} = (&\text{free nicotine[µmol/L]} + \text{nicotine-glucuronide[µmol/L]} \\ &+ \text{free cotinine[µmol/L]} + \text{cotinine-glucuronide[µmol/L]} \\ &+ \text{free trans-3'-hydroxycotinine[µmol/L]} \\ &+ \text{trans-3'-hydroxycotinine-glucuronide[µmol/L]}) \\ &* 162.2[\text{µg/µmol}] \,/\, 1000[\text{µg/mg}]\end{aligned}$$

All concentrations must be in [µmol/L] before applying the above formula. The molecular weights and associated conversion factors from ng/mL to nmol/L are as follows:

Free nicotine	The molecular weight is 162.23 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:54-11-5 [6]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 6.164.
Nicotine-glucuronide	The molecular weight is 338.36 g/mol (National Center for Biotechnology Information (NCBI). PubChem RN:152306-59-7 [7]).

	Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.955.
Free cotinine	The molecular weight is 176.21 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:486-56-6 [8]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.675.
Cotinine-glucuronide	The molecular weight is 352.34 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:139427-57-9 [9]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.838.
Free trans-3'-hydroxycotinine	The molecular weight is 192.21 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:34834-67-8 [10]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.203.
Trans-3'-hydroxycotinine-glucuronide	The molecular weight is 368.34 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:132929-88-5 [11]). Therefore, to convert from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.715.

The adjustment of NEQ for creatinine in urine will be calculated as described in 5.1.

5.2 Questionnaires

5.2.1 Nicotine/Tobacco Product Use History

At the Screening visit and at Admission (Day -2), subjects will be asked questions about their TNP use history. The questions will capture frequency and quantity TNP use over the past 4 weeks, and number of continuous years of CIG smoking. This information will be used to assess subjects' eligibility to participate in the study, and to serve as baseline values.

5.2.2 Fagerström Test for Nicotine Dependence (Revised Version)

Level of nicotine dependence will be assessed using a self-reported questionnaire on Baseline Day -1, using the Fagerström Test for Nicotine Dependence (FTND) in its revised version [12].

The questionnaire consists of six questions which will be answered by the subjects themselves. The scores obtained on the test permit the classification of nicotine dependence into three

levels: Mild (0-3 points), moderate (4-6 points), and severe (7-10 points) [12]. This information will be used as characteristics of the study subjects (see Appendix 13.2).

5.2.3 ABOUT – Product Experience Questionnaire

Product experience will be assessed via a subject self-reported outcome measure, part of the ABOUT toolbox [13]. The questionnaire consists of 3 multi-item scales and 2 single-item scales, arising from an adaptation and rewording of the modified cigarette evaluation questionnaire (mCEQ) [14] to Reduced Risk Products (RRPs) and the Product Evaluation Scale [15]. The questionnaire assesses the degree to which subjects experience the reinforcing effects of P4M3 Gen 2.0 with CA35 and CM 35 Cartridges use in CIG smokers switching to P4M3 compared to subjects continuing CIG smoking by measuring:

- Product satisfaction (satisfying, tastes good, enjoy the product), average of the item scores to questions 1, 2, and 12.
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger), average of the item scores to questions 4, 5, 6, 7, and 8.
- Aversion (dizziness, nausea), average of the item scores to questions 9 and 10.
- Enjoyment of respiratory tract sensations (single-item assessment), item 3.
- Craving reduction (single-item assessment), item 11.

Subjects will be asked to assess the items of the questionnaire on a 7-point scale, ranging from 1= “not at all” to 7= “extremely”.

Symptoms or worsening of symptoms documented in the questionnaire do not need to be documented as additional AEs as the main source for AE collection will be the face-to-face interview between the subject and study site staff, using open, non-directive questions.

5.3 Categorical Variables

P4M3 Gen 2.0 is an ENDS utilizing tobacco sticks with two flavour variants in the corresponding randomization arms, CA35 (“Classic Auburn”) and CM35 (“Classic Menthol”), that will be compared to CIG (conventional cigarette; primary comparison), and SA (smoking abstinence; exploratory comparison) groups.

Table 7 Categorical Variable Definitions

Variable	Categories	Details

Sex	Female Male		Stratification factor used for randomization and statistical analysis
Race	American Indian OR Alaska Native Asian Black Native Hawaiian OR Other Pacific Islander White		Stratification factor used for statistical analysis
BMI (kg/m^2)	Normal Overweight Obese Note that patients with BMI <18.5 (underweight) and ≥ 32 (Obese) are excluded from the study as per the inclusion/exclusion criteria.	≥ 18.5 and < 25.0 ≥ 25.0 and < 30.0 ≥ 30.0 and < 32.0	Derived
FTND total score	Mild: 0-3 Moderate: 4-6 Severe: 7-10		Derived

5.4 Human Puffing Topography

Prior to calculation of the per-day parameters, the topography data will be processed by PMI through analysis software. Only valid data will contribute to the per-puff parameters (listed in Table 4) and will be part of the study database.

Per subject, the per-puff parameters (listed in 4) part of the study database will be used to derive the per-day parameters listed in Table 5 (using the formulas contained in that table).

5.5 CYP1A2

CYP1A2 activity will be assessed in plasma by measuring paraxanthine (PX) and caffeine (CAF) concentrations and calculating the PX/CAF molar metabolic ratio, both expressed in molar equivalent (nmol/L), and calculated as follows:

$$\frac{\text{PX}}{\text{CAF}} = ((\text{PX}_c[\text{ng/mL}]/180.17\ [\text{ng/nmol}]) * [1000\text{mL/L}]) \,/\, ((\text{CAF}_c\ [\text{ng/mL}]/194.19\ [\text{ng/nmol}]) * [1000\text{mL/L}])$$

PX The molecular weight is 180.16 g/mol (National Center for Biotechnology Information (NCBI). PubChem CAS:611-59-6 [16]).

CAF The molecular weight is 194.19 g/mol. (National Center for Biotechnology Information (NCBI). PubChem CAS:58-08-2 [17]).

The converted results will be reported as a percentage.

6 SAMPLE SIZE JUSTIFICATION

In this study, 72 subjects are randomized as follows:

- 36 in combined P4M3 arms (18 in CA35 and 18 in CM35),
- 18 in CIG arm,
- 18 in SA arm.

Based on four previous similar studies conducted by PMI on the tobacco heating system (another alternative product to CIG developed by PMI which is likely to be less risky than cigarette; ClinicalTrials.gov identifiers are NCT01970995, NCT01989156, NCT01959932, and NCT01970982, respectively), Table 8 contains estimates of geometric mean ratios (GMR) and associated coefficients of variations (GCV) for the (adjusted) contrast of a tobacco heating system against CIG. The effect of P4M3 is expected to be similar (or better) on the BoExp selected in this study compared to this tobacco heating system. In addition, based on these studies, up to 15% of missing values may be expected for various reasons (e.g., withdrawals, mis-randomization, etc.).

Using the statistics displayed in Table 8, the sample size planned for this study accounting for 15% of missing values (resulting in 30 and 15 subjects in P4M3 combined and CIG arms, respectively), and a one-sided two-sample t-test (on the log-scale) with 2.5% type I error probability, the estimated power for each BoExp is displayed in Table 8. By multiplying the power for each individual BoExp over the four to be tested in the primary hypothesis (per study), a global estimate of power is also obtained.

Note that 10,000 simulations of one-sided two-sample t-test were also conducted to determine the 90 percentiles of the (upper) half-width of the 97.5%-confidence interval (CI) of the ratio between P4M3 and CIG, as well as the 90 percentiles of the upper bounds of these CIs. These are also displayed in Table 8. These provide indications on the expected precision on the estimates of the ratios.

Table 8 Power Computations for Primary Objective

NCT (Region)	Endpoint	GMR (%)	GCV (%)	Power	Overall Power	90%iles of the upper half-width of CI(%)	90%iles of the upper bound of CI (%)
1970995	2CyEMA	18.23	32.43	>99%	>99%	4.9	25.4
(JP)	3-HPMA	50.67	32.72	>99%		13.8	71
	COHb	44.94	17.24	>99%		6	53.8
	Total NNAL	43.69	26.09	>99%		9.2	57.1
1989156	2CyEMA	17.23	42.01	>99%	>99%	6.2	26.3
(US)	3-HPMA	45.77	36.45	>99%		14.1	66.3
	COHb	38.14	26.5	>99%		8.2	50.3
	Total NNAL	43.81	40.7	>99%		15.3	65.9
1959932	2CyEMA	13.16	34.41	>99%	>99%	3.8	18.7
(EU)	3-HPMA	41.63	26.1	>99%		8.7	54.4
	COHb	23.45	16.84	>99%		3.1	28
	Total NNAL	43.54	27.13	>99%		9.6	57.5
1970982	2CyEMA	21.21	43.16	>99%	>99%	7.9	32.7
(JP)	3-HPMA	52.86	39.57	>99%		17.8	78.9
	COHb	47.1	16.08	>99%		5.8	55.6
	Total NNAL	49.03	42.51	>99%		18	75.3

Table 8 shows that the power of this study for the primary objective is expected to be at least 99%.

A similar reasoning and assumptions for the 1st key secondary objective can be made. Table 9 displays the power estimates for the 1st key secondary hypothesis with a power of at least 99%.

Table 9 Power Computation for 1st Key Secondary Objective

NCT (Region)	Endpoint	GMR (%)	GCV (%)	Power	Overall Power	90%iles of the upper half-width of CI (%)	90%iles of the upper bound of CI (%)
1970995	3-HMPMA	43.06	35.59	>99%	>98%	12.9	62
(JP)	3-OH-B[a]	27.19	43.93	>99%		10.4	42
	S-PMA	10.97	46.63	>99%		4.5	17.4
	Total NNN	27.02	61.84	>99%		15.5	49.1
1989156	3-HMPMA	38.26	53.56	>99%	>98%	18.4	64.6
(US)	3-OH-B[a]	28.94	54.77	>99%		14.3	49.4

	S-PMA	12.58	69.68	>99%		8.4	24.4
	Total NNN	14.06	78.93	>99%		10.8	29.1
1959932	3-HMPMA	22.54	30.76	>99%	>98%	5.7	30.9
(EU)	3-OH-B[a]	27.5	46.17	>99%		11.1	43.5
	S-PMA	5.99	37.3	>99%		1.9	8.8
	Total NNN	24.12	95.15	>99%		22.9	55.7
1970982	3-HMPMA	37.71	49.07	>99%	>98%	16.4	61.6
(JP)	3-OH-B[a]	29.99	52.2	>99%		14	50.2
	S-PMA	15.68	49.76	>99%		6.9	25.6
	Total NNN	30.06	67.69	>99%		19.2	57.4

For the key secondary objectives 2 to 5, a similar reasoning is applied, but this time, a sample of size of 15 for the P4M3 (CA35 or CM35) arms needs to be used and 15 subjects in the CIG arm (with 15 subjects) (Table 10 and Table 11). As per Table 10 and Table 11, the power was at least of 99% for each BoExp in the previous studies.

By multiplying the power for each objective (≈ 99%) across all 6 objectives (1 primary + 5 key secondary), the power for all objectives altogether is then estimated to be at least 94% (= $0.94 \approx 0.99^6$, assuming independence of the 6 objectives, each with a 99% power).

Table 10 Power Computations for Key Secondary Objectives 2 & 4

NCT (Region)	Endpoint	GMR (%)	GCV (%)	Power	Overall Power	90%iles of the upper half-width of CI (%)	90%iles of the upper bound of CI (%)
1970995	2CyEMA	18.23	32.43	>99%	>95%	6.1	26.9
(JP)	3-HPMA	50.67	32.72	>99%		17.2	75.2
	COHb	44.94	17.24	>99%		7.3	55.4
	Total NNAL	43.69	26.09	>99%		11.3	59.7
1989156	2CyEMA	17.23	42.01	>99%	>95%	7.8	28.3
(US)	3-HPMA	45.77	36.45	>99%		17.5	70.7
	COHb	38.14	26.5	>99%		10.1	52.7
	Total NNAL	43.81	40.7	>99%		19.3	71
1959932	2CyEMA	13.16	34.41	>99%	>95%	4.7	19.8
(EU)	3-HPMA	41.63	26.1	>99%		10.8	56.9
	COHb	23.45	16.84	>99%		3.7	28.8
	Total NNAL	43.54	27.13	>99%		11.9	60.4
1970982	2CyEMA	21.21	43.16	>99%	>95%	9.9	35
(JP)	3-HPMA	52.86	39.57	>99%		22.4	84.4

COHb	47.1	16.08	>99%	7.1	57.2
Total NNAL	49.03	42.51	>99%	22.5	80.9

Table 11 Power Computations for Key Secondary Objectives 3 & 5

NCT (Region)	Endpoint	GMR (%)	GCV (%)	Power	Overall Power	90%iles of the upper half-width of CI (%)	90%iles of the upper bound of CI (%)
1970995	3-HMPMA	43.06	35.59	>99%	>94%	16.0	65.9
(JP)	3-OH-B[a]	27.19	43.93	>99%		13.0	45.2
	S-PMA	10.97	46.63	>99%		5.6	18.9
	Total NNN	27.02	61.84	>99%		19.8	54.2
1989156	3-HMPMA	38.26	53.56	>99%	>94%	23.2	70.4
(US)	3-OH-B[a]	28.94	54.77	>99%		18.2	54.2
	S-PMA	12.58	69.68	>99%		10.7	27.3
	Total NNN	14.06	78.93	>99%		14.0	33.1
1959932	3-HMPMA	22.54	30.76	>99%	>94%	7.1	32.6
(EU)	3-OH-B[a]	27.5	46.17	>99%		14.0	47.2
	S-PMA	5.99	37.3	>99%		2.4	9.3
	Total NNN	24.12	95.15	>99%		30.0	64.6
1970982	3-HMPMA	37.71	49.07	>99%	>94%	20.6	66.5
(JP)	3-OH-B[a]	29.99	52.2	>99%		17.8	55.1
	S-PMA	45.68	49.76	>99%		8.8	27.9
	Total NNN	30.06	57.69	>99%		24.6	63.8

7 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

- Addition of the definition of the Screened Population,
- Clarification of the Per Protocol Set (PPS),
- Clarification of the Safety Set (SAF),
- Clarification on safety follow-up periods:
  - Exposure period ends either on Day 5, 11:00 PM or early discontinuation date and time,
  - Follow-up period starts with end of exposure.

8 ANALYSIS SETS

8.1 Screened Population

The Screened Population consists of all subjects who signed the ICF and who underwent at least one of the screening procedures.

8.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all randomized subjects who have at least one post-randomization product use experience (if randomized to CIG or one of the P4M3 arms) and who have at least one valid non-safety assessment. The FAS will be analyzed by randomized study arm.

8.3 Per Protocol Set (PPS)

The Per Protocol Set (PPS) is a subset of FAS and includes all randomized subjects who fulfil key compliance criteria of the protocol, i.e., have no major protocol deviation impacting the evaluability of the primary objective. The PPS will be analyzed by randomized study arm.

8.4 Safety Set (SAF)

The Safety Set (SAF) population will consist of all the subjects with at least one exposure to P4M3 (product test at Admission Day -2), and who have at least 1 valid value for a safety assessment. The SAF will be analyzed according to randomized study arm or a group of enrolled but not randomized subjects when applicable (there is an exception to this rule and mis-randomized subjects will be assigned to their actual exposure arm, see Table 12).

8.5 Protocol Deviations

Protocol Deviations will be summarized by major and minor categories for the PPS, FAS and SAF. All Protocol Deviation data will be listed.

8.5.1 Major Protocol Deviations

Protocol deviations are defined as any departure from the procedures defined in the protocol. Major deviations will include, but are not limited to the categories outlined in Table 12:

Table 12 Major Protocol Deviations with Impact on Evaluability

Category	Description
Any violation of inclusion/exclusion criteria	Considered a major deviation. The blinded data review team will decide on whether it impacts evaluability.
Mis-randomization (wrong information provided to randomization system)	Considered a major deviation with impact on evaluability. Mis-randomized subjects will be classified according to their actual exposure arm for safety analysis.
Use of any nicotine or tobacco-containing product other than the assigned product during the exposure period	Considered a major deviation. The blinded data review team will decide on whether it impacts evaluability.
Assessments related to the primary objective performed outside the time tolerance (see Table 13)	Considered a major deviation. The blinded data review team will decide on whether it impacts evaluability.

8.5.2 Minor Protocol Deviations

Minor deviations may include, but are not limited to, use of concomitant medication and assessments performed outside the time tolerance (see Table 13).

8.5.3 Assessment Time Points and Assessment Time Windows

Table 13 contains the list of assessments that have a time constraint and an acceptable tolerance.

Table 13 Assessment Time Constraints and Time Windows

Related to Primary Objective	Assessment	Time constraint	Tolerance

Yes	Blood sample at days -1 and 6 or during early termination visit	After >= 6 hours of fasting	Not applicable
No	CYP1A2 activity at days -1 and 5	Collection of blood sample 6 hours after intake of caffeine tablet	+/- 15 minutes
Yes	24-hours urine	24h	+/- 1 hour

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical evaluation will be performed using SAS®, version 9.4 or later.

9.1.1 Stratified Presentation

Sex (male and female) is used as a stratification factor during randomization and for the presentation of descriptive statistics. Race will also be used as stratification factor for the presentation of the descriptive statistics.

9.1.2 Sub-group Analyses

No further sub-group analyses are planned.

9.1.3 Descriptive Statistics

All data will be presented in listings, ordered by randomization arm, subject, and study day unless otherwise specified.

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), 95% confidence interval (CI) of the arithmetic mean, median, first and third quartiles, minimum, maximum; for log-normal data, the geometric mean, geometric coefficient of variation (CV), and 95% CI of the geometric mean will be presented in addition.

Post-baseline summaries will include change from baseline apart from log-normal variables which will percentage change from baseline.

When applicable, the number and percentage of subjects with values below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) will also be presented.

For categorical variables frequency counts (n) and percentages (%) will be presented. The number and percentage of subjects with missing data will also be presented.

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

Unless specified otherwise the denominator for percentages will be the total number of subjects in each respective group except missing data.

9.1.4 Definitions for Statistical Data Analysis

At the time of the present protocol, no new terms are defined.

9.1.5 Handling of Dropouts or Missing Data

9.1.5.1 Laboratory Parameters

Values outside detection limits will be substituted using the following rules (e.g., for BoExp parameters):

- Values below LLOQ will be imputed using LLOQ/2.
- Values above ULOQ will be imputed using ULOQ.

Unless otherwise stated, other missing values will not be imputed.

9.1.5.2 Questionnaires

Missing data will be handled as follows for the ABOUT – Product Experience Questionnaire.

If there are more than or equal to 50% of within-person item-level missing data within a domain/scale, the missing item-levels will be kept as missing, and the domain/scale score will be set to missing. If there are less than 50% of within-person item-level missing data within a domain/scale, the following rule will be used to produce a complete within-person response pattern:

1. Sum the available within-person item responses and divide that score by the number of items which have responses.

2. Replace the items with missing responses with the within-person mean.

3. Calculate a domain/scale score to two significant digits by using all items and the standard formula used when all items are not missing.

For the Fagerström Test for Nicotine Dependence Questionnaire, the total score is set to missing if any of the items is missing (see Appendix 13.2). No imputation of missing value will be done for the Nicotine/Tobacco Product Use History Questionnaire.

9.1.5.3 Missing or Partial Dates

Dates missing or partial will not be imputed for AEs, medical history, and concomitant medications, but the following assumptions will be made to assign them to categories:

Date Information	AE Category	Disease Category	Medication Category
If the date is completely missing, or for partial dates, if the month/year is the same as, or later than the month and/or year of screening	NA	Concomitant Disease	Concomitant Medication
For partial dates, if the month/year is earlier than the month and/or year of screening	NA	Medical History	Prior Medication

9.1.5.4 Insufficient Data for Analysis/Presentation

If there are no values or events for a planned output, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No adverse events related to study procedures occurred for this study”.

For stratified analyses, strata with <5 subjects overall will not be presented.

9.1.6 Handling of Unplanned Data

If any unplanned assessments do occur, they will be included in listings only. Only planned assessments will be summarized.

9.1.7 Multiple Comparison/Multiplicity

Overall family-wise type I error will be preserved at the α-level of 2.5% (1-sided tests will be conducted for the primary and key secondary study hypotheses). This will be done by using a fixed sequence of testing: primary objective → 1st key secondary objective → 2nd key secondary objective → 3rd key secondary objective → 4th key secondary objective → 5th key secondary objective. All objectives will be tested sequentially in a given order at the 2.5% type I error level until one of the objectives is rejected in which case all subsequent testing will be exploratory 2-sided tests at an α-level of 5%, and the associated 2-sided 95% confidence interval will be reported.

The primary study hypothesis will be tested 1-sided with a type I error α-level of 2.5%. The associated 1-sided 97.5% confidence interval will be provided. This will be applied to all BoExps of Table 1 that are part of the primary study hypothesis. Subsequent analyses of objectives will only proceed if this hypothesis is not rejected.

If the primary study hypothesis is not rejected, the same α-level of 2.5% will be used for the 1st key secondary hypothesis and the associated 1-sided 97.5% confidence interval will be reported. This will be applied to all BoExps of Table 2 that are part of the 1st key secondary hypothesis. Subsequent analyses will only proceed if the hypothesis is not rejected.

The analysis will proceed in a similar way for the following key secondary objectives.

For all the exploratory objectives, the statistical tests will be 2-sided with an α-level of 5%. Associated 2-sided 95% confidence intervals will be provided.

9.2 Disposition of Subjects

The number of subjects screened will be provided. The number and percentage (based on the number of subjects screened) of screen failures will also be provided, as well as the reasons for screen failures. The number and percentage (based on the number of subjects screened) of enrolled but not randomized subjects will also be reported.

Randomized subject disposition will be summarized by absolute counts (n) and percentages (%) and split by randomization arm and overall. Percentages will be based on the number of subjects in each randomization arm or overall. The number of subjects who completed the study, the number of subjects who prematurely discontinued, and the primary reason for withdrawal will be reported.

Disposition data will be listed.

9.3 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized as follows:

- By randomized study arm for the FAS
- By randomized study arm for the PPS
- By randomized study arm or a group of enrolled but not randomized subjects when applicable for the SAF

Demographic variables will include sex, age (years), race, body weight (kg), height (m), body mass index (BMI, kg/m^2). Body weight and BMI will be summarized at screening and admission. Baseline characteristics include TNP use history (average product use per day in the last four weeks, number of participants with continuous product use for the past 3 years, and other questions included in the Nicotine/Tobacco Product Use History questionnaire), spirometry measurements (FEV1, FEV1 % predicted, FVC, FVC % predicted, and FEV1/FVC), and FTND questionnaire score.

All demographic and baseline characteristics data will also be summarized using the stratification factors provided in section 9.1.1.

All demographic and baseline characteristics data will be listed.

9.4 Measurement of Product Compliance

The distribution and return of the P4M3 components (P4M3 Battery Unit and P4M3 Cartridge) will be documented in appropriate logs. CIG butts will be collected and documented for accountability. These data will be presented in listings.

9.5 Extent of Exposure (Product Consumption)

All subjects in the P4M3 (both CA35 and CM35) and CIG arms will be permitted *ad libitum* use of the respective products, while the SA arm will abstain from CIG smoking.

This data will be summarised for the FAS, PPS, and SAF, as well as stratified using the factors described in section 9.1.1, as follows:

For the CIG group, the following parameters will be summarized:

- Number of cigarette butts and percent change from baseline for Day 1, 2, 3, 4, 5,
- Average number of cigarette butts per day (computed using the sum of all cigarette butts collected over Days 1-5 divided by the number of days spent by the subject in the exposure period) and percent change from baseline,

- Total cigarette butts over 5 days.

For the P4M3 CA35 and P4M3 CM35 groups, the following parameters will be summarized:

- Number of cartridges for Day 1, 2, 3, 4, 5,
- Average number of cartridges used per day (computed using the sum of all cartridges used over Days 1-5 and divided by the number of days spent by the subject in the exposure period),
- Total number of cartridges used over 5 days.,
- Weight of e-liquid used per day for Day 1, 2, 3, 4, 5 (where weight is calculated as post-product use cartridge weight subtracted from pre-product use cartridge weight in mg),
- Average weight of e-liquid used per day (computed using the sum of all weights of e-liquid used over Days 1-5 and divided by the number of days spent by the subject in the exposure period),
- Total weight of e-liquid used over 5 days.

All exposure data will also be listed.

9.6 Planned Statistical Analyses

9.6.1 Primary Objective: Primary Estimand Analysis

The primary objective of the study is to demonstrate the reduction of BoExp to selected HPHC in smokers switching from CIG to P4M3 (combined CA35 and CM35 arms) compared to continuing CIG smoking for 5 days.

9.6.1.1 Primary Estimand

The primary estimand of the primary objective is defined by the following components:

- Product Use Under Evaluation: This corresponds to the study arms (CIG, P4M3 CA35, P4M3 CM35, or SA) randomly allocated to subjects and for which they have fulfilled key compliance criteria of the protocol, i.e., without major protocol deviations that impact the evaluability of the primary objective (as defined by the PPS).
- Target Population: This is the population of adult smokers who satisfy all eligibility criteria.
- Variables of Interest: 3-HPMA, 2CyEMA, total NNAL (all expressed as concentration adjusted for creatinine in 24-hour urine), and COHb (expressed as % of saturation of hemoglobin).

- Intercurrent Events (ICEs):
  - Non-adherences to the randomization arm: these ICEs are out of scope of this primary estimand, and related subjects will be excluded from this analysis.
  - Study discontinuation and death: data related to subjects who discontinued or died during the exposure period will be included only if they were adherent until the time of discontinuation/death.
  - Subjects that test COVID-19 positive during the study: subjects will be included only until the time of the diagnosis or vaccination. Data collected after or at the date of the COVID-19 positive test will be reported as missing.
  - Changes in comorbidities: subjects with comorbidities or worsening of an existing comorbidity will be included as this change may be linked to the reduction or modification of their CIG consumption.
- Population-Level Summary Statistic: geometric mean ratios between P4M3 (CA35 and CM35 combined) and CIG of the BoExp under consideration at Day 5.

9.6.1.2 Main Analysis

The primary analysis will be a mixed model for repeated measures (MMRM) conducted with the PPS. An unstructured matrix will be used to model the variance-covariance structure within subjects. If this model fails to converge, then the following variance-covariance matrices will be used (in order) until one converges: Heterogeneous Toeplitz, Heterogeneous First Order Autoregressive, Heterogeneous Compound Symmetry, Variance Components, Compound Symmetry, and finally no repeated statement.

The model for the endpoint expressed on the log-scale will adjust for the endpoint value at baseline (log-scale), Day, randomization arm, and its interaction with Day, and sex. The model described above will be implemented in the SAS® language as:

```
PROC MIXED data=dataset method=reml nobound;
        class Arm Day Subject Sex;
        model Log(Endpoint) = Log(Baseline) Day Arm Arm*Day
                Sex / ddfm=kenwardroger2 solution;
        repeated Day / subject=Subject(Arm) type=un rcorr;
        lsmeans Arm*Day / pdiff cl;
        lsmestimate 'Contrast P4M3 (CA35 and CM35 combined) vs. CIG' exact syntax to be
adjusted depending on the coding of class variables / cl upper alpha=0.025;
        lsmestimate 'Contrast P4M3 CA35 alone vs. CIG' exact syntax to be adjusted depending
on the coding of class variables / cl upper alpha=0.025;
        lsmestimate 'Contrast P4M3 CM35 alone vs. CIG' exact syntax to be adjusted depending
on the coding of class variables / cl upper alpha=0.025;
RUN;
```

LS-means per randomization arm and day will be obtained (on the log-scale), as well as pairwise differences between arms per day, together with their 95%-confidence intervals and (unadjusted) p-values. Exponentiation of these quantities will lead to the geometric LS-means per randomization arm and (geometric) ratios between arms with their associated 95%-confidence intervals.

The exponentiation of the 'lsmestimate' statement above entitled 'Contrast P4M3 (CA35 and CM35 combined) vs. CIG' will allow contrasting the two P4M3 Gen 2.0 CA35 and CM35 study arms combined against the CIG arm and will be used to assess the primary study hypotheses. Similarly, the exponentiation of the two subsequent 'lsmestimate' statements will be used to assess the key secondary objectives 2 and 4 if the procedure of fixed sequence testing allows it.

For each individual BoExp in the Primary Analysis, the hypothesis will be evaluated using the 1-sided statistical test with a type I error level of 2.5% given by the 'lsmestimate' statement 'Contrast P4M3 (CA35 and CM35 combined) vs. CIG' of the model described in this section.

The study will be declared successful if the ratio of the geometric means between P4M3 (CA35 and CM35 combined) over CIG is statistically lower than 1 at Day 5 for all four Primary BoExp.

9.6.1.3 Supportive/Sensitivity Analyses

The model described in section 9.6.1.2 will be used to contrast all randomization arms at Days 1, 2, 3, 4, and 5. Pairwise comparisons at Days 1, 2, 3, 4, and 5 will be reported, together with their unadjusted p-values and 95%-confidence interval:

- P4M3 (CA35 and CM35 combined) vs. CIG
- SA vs. CIG
- P4M3 (CA35 and CM35 combined) vs. SA
- P4M3 CA35 vs. CIG
- P4M3 CM35 vs. CIG
- P4M3 CA35 vs. SA
- P4M3 CM35 vs. SA
- P4M3 CA35 vs. P4M3 CM35

Contrasts P4M3 CA35 vs. CIG and P4M3 CM35 vs. CIG will also be estimated one-sided with a type I error level of 2.5% through the additional 'lsmestimate' statements. These contrasts will be used to assess the key secondary objectives 2 and 4 if the procedure of fixed sequence testing (see section 9.6.3) allows.

Descriptive statistics as mentioned in section 9.1.3 for the variables of interest and associated changes from baseline will be reported by randomization study arm for the PPS and by study day. Descriptive statistics stratified by the factor described in section 9.1.1 will also be computed.

9.6.2 Primary Objective: Secondary Estimand Analysis

9.6.2.1 Secondary Estimand

This analysis refers to the secondary estimand of the primary objective. This estimand will implement the "treatment policy strategy" and reflects the intention-to-treat (ITT) principle. It will evaluate the effect of switching to P4M3 as compared to continuing to smoke CIG in the FAS rather than in the PPS. It is defined by the following components:

- Product Use Under Evaluation: This corresponds to the study arm (CIG, P4M3 CA35, P4M3 CM35, or SA) randomly allocated to subjects and is independent of whether subjects were adherent or not (FAS).
- Target Population: This is the population of adult smokers who satisfy all eligibility criteria.
- Variables of Interest: 3-HPMA, 2CyEMA, total NNAL (all expressed as concentration adjusted for creatinine in 24-hour urine), and COHb (expressed as % of saturation of hemoglobin).
- Intercurrent Events (ICEs): All ICEs will be treated as 'treatment policy strategy'. This means that the values of the variable of interest is used regardless of whether the ICEs occur.
- Population-Level Summary Statistic: Geometric mean ratios between P4M3 (CA35 and CM35 combined) and CIG of the BoExp under consideration at Day 5

9.6.2.2 Main Analysis

This analysis will be conducted using the same model as the one described in section 9.6.1.2, except that it will use the FAS instead of the PPS and all available data will be included in the model.

In section 9.6.1.2, the criterion to declare the study successful was provided. Here, the same difference will be computed and interpreted exploratorily using the same type I error level as for the primary confirmatory hypothesis.

9.6.2.3 Supplementary Analysis

Randomized study arms will be contrasted at Days 1, 2, 3, 4, and 5. Pairwise comparisons at Days 1, 2, 3, 4, and 5 will be reported, together with their unadjusted p-values and 95%-confidence interval:

- P4M3 (CA35 and CM35 combined) vs. CIG
- SA vs. CIG
- P4M3 (CA35 and CM35 combined) vs. SA
- P4M3 CA35 vs. CIG
- P4M3 CM35 vs. CIG
- P4M3 CA35 vs. SA
- P4M3 CM35 vs. SA
- P4M3 CA35 vs. P4M3 CM35

As in the primary estimand analysis, the contrasts P4M3 CA35 vs. CIG and P4M3 CM35 vs. CIG will also be estimated one-sided with a type I error level of 2.5% through the additional 'lsmestimate' statements provided in section 9.6.1.2. These contrasts will be used exploratorily to assess the key secondary objectives 2 and 4 if the procedure of fixed sequence testing allows.

Descriptive statistics as mentioned in section 9.1.3 for the variables of interest and associated changes from baseline will be reported by randomization study arm for the FAS and by study day. Descriptive statistics stratified by the factor described in section 9.1.1 will also be computed.

9.6.3 Secondary Objective Analyses

9.6.3.1 Key Secondary Objectives

The 1st key secondary objective of the study is to demonstrate the reduction of Secondary BoExps to selected HPHC in smokers who switch from CIGs to P4M3 use compared to those who continue to smoke CIG. The analyses used for the primary and secondary estimands will be repeated with the Secondary BoExp endpoints.

Subsequent key secondary objectives (from 2 to 5) will use the statistical models developed to assess the primary and 1st key secondary objectives, except that they will contrast either CA35 vs. CIG or CM35 vs. CIG (instead of CA35 and CM35 combined vs. CIG).

The evaluation of the key secondary objectives will be done using a procedure of fixed sequence testing as specified in Figure 2. This first key secondary objective will only be tested

if the primary objective is demonstrated, which preserves the study-wise type I error rate at the 2.5%. An additional benefit will be declared if the ratio of the geometric means between P4M3 (CA35 and CM35 combined) over CIG is statistically lower than 1 at day 5 for all four additional key secondary BoExp.

If both the primary and first key secondary objectives are successful, then the 2nd key secondary objective will be tested with type I error level of 2.5%, and similarly in sequence until objective 6 (Figure 2). If, during subsequent tests, any of the objectives are not successful, the sequence testing will stop, and further testing will cease. Specifically, if the hypothesis for a single BoExp is rejected, then the fixed sequence testing will stop.

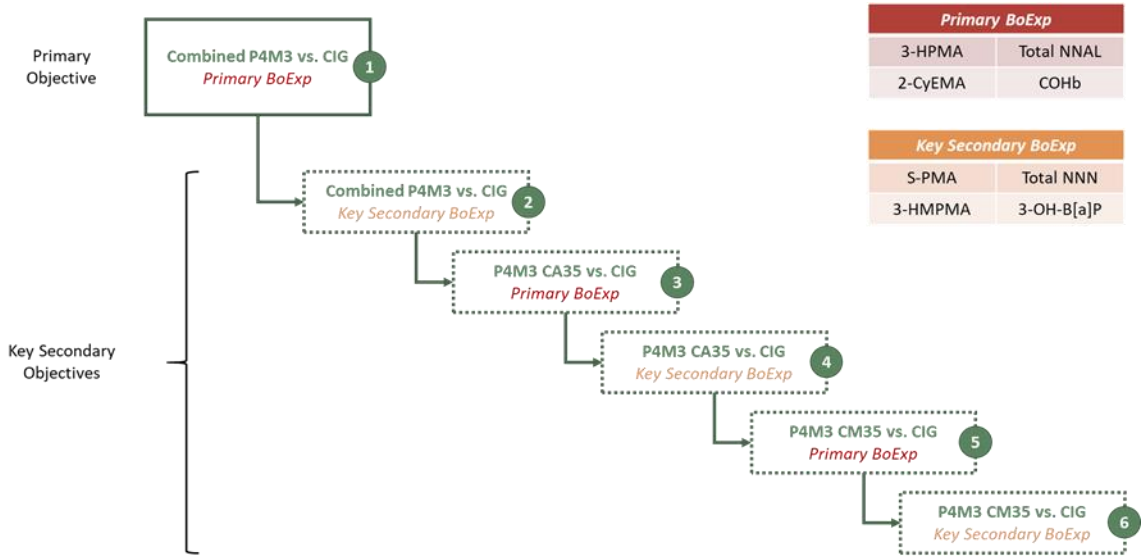


Figure 2 Representation of the Procedure of Fixed Sequence Testing

9.6.3.2 Secondary Objective

The secondary objective of this study is to monitor safety and tolerability in all subjects during the study. All safety analyses will be conducted with the SAF (inferential analyses will not be performed on safety endpoints) and are described in 9.6.5.

9.6.4 Exploratory Analyses

The exploratory analyses will be conducted using both the FAS and the PPS. Descriptive statistics as described in 9.1.3 will be provided, unstratified, and also using the stratification factors displayed in section 9.1.1. All data (collected and derived) will be listed.

9.6.4.1 Exploratory Objective 1: Additional BoExp

The statistical analyses described in 9.6.1 and 9.6.2 will be repeated using the BoExp listed in Table 3 (without success criteria). Endpoints are assumed to be log-normally distributed, and the natural logarithm of the values will be used (the statistical model will then use the natural logarithm of the baseline as covariate). The results will then be transformed back to the original scale as was done for the BoExp used in the context of the evaluation of the primary and key secondary objectives.

9.6.4.2 Exploratory Objective 2: Comparison with SA

The comparison of the SA arm against CIG and P4M3 (CA35 and CM35 arms combined and separately) on BoExp listed in Table 1, Table 2, and Table 3 will be covered by the statistics computed in sections 9.6.1, 9.6.2, 9.6.3.1, and 9.6.4.1.

9.6.4.3 Exploratory Objective 3: Nicotine/Tobacco Product Use

The exploratory objective 3 related to the nicotine/product use will be covered by the statistics computed as described in section 9.5.

9.6.4.4 Exploratory Objective 4: ABOUT – Product Experience

Data from each item of the ABOUT – Product Experience questionnaire will be summarised as categorical (each possible level per item will be displayed). Subscales will be considered as continuous and summarized accordingly.

9.6.4.5 Exploratory Objective 5: Human Puffing Topography

Separately for each Day = 1, 2, 3, 4, and 5, the per-day parameters (Table 5) will be considered as continuous variables and summarised as described in section 9.1.3 on the P4M3 arm (CA35 or CM35 combined and separately), except that no change from baseline can be computed.

For each subject, the per-day parameters (Table 5) will be averaged over days 1-5. These averages per subject will then be considered as continuous variables and summarised as described in section 9.1.3 on the P4M3 arm (CA35 or CM35 combined and separately), except that no change from baseline can be computed.

9.6.4.6 Exploratory Objective 6: CYP1A2 Enzymatic Activity

In this study, the CYP1A2 enzymatic activity will be calculated using the molar ratio of PX and CAF, as described in section 5.5.

The statistical analyses described in 9.6.1 and 9.6.2 will be repeated using the CYP1A2 enzymatic activity expressed as % as endpoint (no logarithmic transformation will be performed). Because CYP1A2 enzymatic activity will only be measured at baseline and Day 5, the REPEATED statement in the model becomes irrelevant and will not be included. Similarly, the terms Day and Arm*Day in the MODEL statement will be removed and the LSMEANS statement will use Arm instead of Arm*Day.

9.6.5 Safety Evaluation

9.6.5.1 Adverse Events

AEs (including SAEs) will be collected from the time of ICF signature until the EOS for each participant (AEs occurring on subjects who are not part of the SAF will only be listed and are not part of the summaries related to SAF).

Any AEs which may occur during the screening period will be captured by the investigational site staff and assessed by the Investigator or designee(s) to establish relationship to study procedures.

During a 3-day Safety follow-up period new AEs/SAEs will be recorded and ongoing AEs/SAEs will be followed-up by the study site.

Information recorded for AEs/SAEs will include verbatim description, start and stop dates and times, seriousness, severity (intensity), causal relationship with IP and study procedures, action taken with IP (e.g., reduced, not changed), other action taken (e.g., treatment administered, if led to the subject's discontinuation from the study), and outcome (e.g., resolved, stabilized).

All safety data will be provided in listings by randomized study arm or a group of enrolled but not randomized subjects, subject, and safety period. The safety periods are defined as:

- Screening: from Screening visit to baseline
- Exposure: from Day 1 to Day 5 11:00 PM or early discontinuation date and time
- Follow-up: from end of exposure to end of Safety follow-up

Unless otherwise specified, summaries will be produced by randomized study arm or a group of enrolled but not randomized subjects and safety periods.

Adverse event data will be used for the primary assessment of safety. Other safety variables monitored in this study will include vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate), ECG data, spirometry data, clinical chemistry, hematology, urine analysis safety panel, concomitant medications.

The number and percentage of subjects with AEs and SAEs will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for the SAF, overall and by safety period. The number of AEs and SAEs by relatedness to product exposure (including expectedness) and relatedness to study procedures, AEs by severity, and AE by action taken related to the product will be summarized. The number of subjects experiencing an event and the number of events for the SAF will be tabulated. Common adverse events will also be tabulated. Common AEs would be those AEs that have PTs with incidence ≥ 5% in any of the randomized study arms or group of enrolled but not randomized subjects.

Unless specified otherwise, results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

9.6.5.1.1 Serious Adverse Events (Including Deaths)

The number and percentages of SAEs will be summarized overall and by SOC and PT for each randomized study arm or a group of enrolled but not randomized subjects when applicable, for the SAF. Tabulations will include both the number of subjects experiencing an event and the number of events.

Unless specified otherwise, results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

The number and percentage of deaths will be presented if applicable and AEs leading to death will be listed.

All SAE data will be listed.

9.6.5.1.2 Adverse Events Leading to Discontinuation

Subjects discontinuing the study due to an AE will undergo the early termination procedures and will enter the 3-day Safety Follow-Up Period. If there are any AEs leading to discontinuation of a product or the study, they will be summarized overall and by SOC and PT for the SAF.

All AEs leading to discontinuation will be listed.

9.6.5.2 Device Events

The number and percentage of subjects with device events, the number and percentage of subjects with device events overall, leading to an AE, an SAE, discontinuation, or to non-adherence will be tabulated for the SAF.

All device events will be listed.

9.6.5.3 Medications, Physical Findings, Vital Signs and Other Observations Related to Safety

9.6.5.3.1 Clinical Laboratory Evaluation

Table 14 details the clinical laboratory parameters.

Table 14 Clinical Laboratory Parameters Safety Panel

Hematology	Clinical Chemistry	Urine Analysis
- Hematocrit	- Albumin	- pH
- Hemoglobin	- Total protein	- Bilirubin
- Mean corpuscular hemoglobin	- Alkaline phosphatase	- Glucose
- Mean corpuscular hemoglobin concentration	- Alanine aminotransferase	- Nitrite
	- Aspartate aminotransferase	- Red blood cell traces
- Mean corpuscular volume	- Blood urea nitrogen	- Protein
- Platelet count	- Creatinine	- Specific gravity
- Red blood cell count	- Gamma-glutamyl transferase	
- White blood cell (WBC) count	- Fasting glucose*	
- Differential WBC count:	- Lactate dehydrogenase	
• Neutrophils	- Potassium	
• Basophils	- Sodium	
• Eosinophils	- Total bilirubin	
• Lymphocytes	- Direct bilirubin	
• Monocytes	- Total cholesterol	
	- Triglycerides	

Descriptive statistics for actual values and changes from baseline will be produced for the clinical chemistry, hematology, and urinalysis safety panel, for the SAF.

All laboratory data will be listed for all subjects.

9.6.5.3.2 Medical History and Concomitant Disease

Medical history (any condition that started and ended prior to the ICF signature at the Screening visit) and concomitant diseases (any condition detected or ongoing at the time of ICF signature) will be coded using MedDRA and listed separately.

Medical history and concomitant diseases will be summarized by randomized study arm or a group of enrolled but not randomized subjects, SOC and PT for the SAF. The number and percentages of subjects with any medical history/concomitant disease will be presented along with the number and percentage of subjects who record each medical history/concomitant disease by SOC and PT. Unless specified otherwise, results will be sorted alphabetically by SOC, and by decreasing frequency of the PTs within a SOC. In the event of PTs having equal frequencies, the PTs will be sorted alphabetically within the SOC.

Medical history and concomitant disease data will be listed for all subjects.

9.6.5.3.3 Prior and Concomitant Medication

All medications will be listed for all enrolled subjects by randomized study arm or a group of enrolled but not randomized subjects when applicable using PT and Anatomical Therapeutic and Chemical (ATC) codes (WHO Drug Global). A flag will be included in the listing to indicate whether the medication is prior or concomitant.

Concomitant medications will be summarized by randomized study arm or a group of enrolled but not randomized subjects for the SAF. The number and percentages of subjects who used the medication at least once will be presented by ATC 1st and 2nd levels and preferred drug name.

9.6.5.3.4 Physical Examination

The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant results will be tabulated for the SAF.

Physical examination data will be listed for all subjects.

9.6.5.3.5 Vital Signs

Actual values and changes from baseline for pulse rate (bpm), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg), respiratory rate (breaths/min), and body temperature (^{o}C) will be summarized as continuous variables (see section 9.1.3) for the SAF.

Vital signs data will be listed for all subjects.

9.6.5.3.6 Spirometry

Actual values and changes from baseline for FEV1, FEV1 % predicted, FVC, FVC % predicted and FEV1/FVC will be summarized as continuous variables (see section 9.1.3) for the SAF.

Spirometry data will be listed for all subjects.

9.6.5.3.7 Electrocardiogram

Actual values and changes from baseline for heart rate (bpm), PR interval (msec), QRS interval (msec), QT interval (msec), and QTcF interval (msec) (corrected according to Fridericia's formula) will be summarized as continuous variables (see section 9.1.3) for the SAF.

Each of ECG parameters mentioned above are classified as being normal, abnormal – clinically significant, abnormal – not clinically significant. The numbers and percentages for these categories, including the combined total abnormal classifications, will be summarized at each visit for the SAF, as described in section 9.1.3. as categorical variables.

ECG data will be listed for all subjects.

9.6.6 Others

Any collected data not included in any of the summaries or listings described above will be listed (e.g., serology).

10 ANALYSES AND REPORTING

10.1 Interim Analyses and Data Monitoring

Not applicable.

10.2 Safety Reporting

AEs will be collected from the time the subjects have signed their ICF until the end of the study. The Investigator must notify the sponsor of all SAEs within 24 hours of the first awareness.

Any pregnancy detected after enrolment must be reported by the Investigator to the sponsor within 24 hours of the first awareness and must be followed-up until the pregnancy outcome is reached.

Expedited reporting of SAEs and, if applicable, pregnancies, to competent authorities will be done as locally required.

Information regarding AEs related to P4M3 product events should be actively collected during the study visits. Furthermore, any events of the P4M3 device that do lead to an AE/SAE will follow the same processes as described above.

10.3 Topline Results

Not applicable.

10.4 Final Analyses

Final analyses for this study will be performed after database lock. A data review meeting will be held prior to database lock. This data review meeting will be done on study data by the unblinded team, and the Protocol Deviation classification will be done on blinded data by blinded team.

Any post-hoc, additional exploratory analyses which were not identified in the SAP will be documented and reported as applicable. Any results from these unplanned analyses will be clearly identified in the CSR.

The list of TFLs to be presented will be provided in the separate TFLs shell document.

10.5 ClinicalTrials.Gov Reporting

Statistical summaries to be evaluated for publishing on the clinical trials.gov website will be flagged in the separate TFLs shell document. For some information that will be highlighted in the separate TFLs shell document, the website requires to display statistics for the overall analysis set in addition to the ones per arm. Those statistics will be computed and added to the corresponding tables.

11 DATA PRESENTATION

Unless specified otherwise in this document, data presentation will be consistent with the PMI style guide.

12 REFERENCES

1. WHO Study Group, et al., *The scientific basis of tobacco product regulation: second report of a WHO study group*. World Health Organ Tech Rep Ser, 2008(951): p. 1-277.
2. U.S. Department of Health and Human Services and FDA (Food and Drug Administration), *[Docket No. FDA-2012-N-0143]: harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list*. Federal Register, 2012. **77**(64): p. 20034-37.
3. FDA (Food and Drug Administration), *Guidance for industry - Reporting harmful and potentially harmful constituents in tobacco products and tobacco smoke under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act - Draft guidance*. 2012.
4. FDA (Food and Drug Administration), *Guidance for industry - Premarket tobacco product applications for electronic nicotine delivery systems*. 2019. **Available from: https://www.fda.gov/media/127853/download (Accessed on 27 September 2019).**
5. FDA (Food and Drug Administration), *Guidance for industry - Patient-reported outcome measures: use in medical product development to support labeling claims*. 2009.
6. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 89594: nicotine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/89594 (Accessed on 24 June 2022).
7. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 3035848: nicotine glucuronide. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/3035848 (Accessed on 24 June 2022).
8. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 854019: cotinine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/854019 (Accessed on 24 June 2022).
9. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 3398121: cotinine glucuronide. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/3398121 (Accessed on 24 June 2022).
10. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 107963: trans-3'-hydroxycotinine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/107963 (Accessed on 24 June 2022).
11. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 53477725: trans-3-hydroxycotinine glucuronide. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/trans-3-Hydroxycotinine-glucuronide (Accessed on 24 June 2022).
12. Fagerström, K., et al., *The Fagerström Test for Nicotine Dependence as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data*. Nicotine and Tobacco Research, 2012. **14**(12): p. 1467-73.

13. Chrea, C., et al., *Developing fit-for-purpose self-report instruments for assessing consumer responses to tobacco and nicotine products: the ABOUT Toolbox initiative*. F1000Res, 2018. **7**: p. 1878.
14. Cappelleri, J.C., et al., *Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire*. Addictive Behaviors, 2007. **32**: p. 912–923.
15. Hatsukami, D.K., et al., *Subjective responses to oral tobacco products: scale validation*. Nicotine Tob Res, 2013. **15**(7): p. 1259-64.
16. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 4687: paraxanthine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/4687 (Accessed on 24 June 2022).
17. National Center for Biotechnology Information (NCBI). PubChem compound summary for CID 2519: caffeine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/2519 (Accessed on 24 June 2022).

13 APPENDICES

13.1 Schedule of Events

	Screening	Confinement Period								Early termination [g]	Safety follow-up [h]
Visit (Time Window)		**Admission** [f]	**Baseline**	**Exposure period**					**Discharge**		**3 days post Discharge**
Study Day	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**		**7 to 9**
Informed consent	•										
Information on the risk of smoking; smoking cessation advice; debriefing	•	•							•	•	
Identification of current CIG brand		•									
Inclusion/exclusion criteria	•	•									
Nicotine/tobacco product use history questionnaire	•	•									
Electrocardiogram (ECG)	•		•						•	•	
Spirometry	•		•						•	•	
Demographics	•										
Medical history, concomitant diseases	•										
Concomitant disease status		•	•	•	•	•	•	•	•	•	
Prior/concomitant medication	•	•	•	•	•	•	•	•	•	•	[i] •

Physical examination	•										
Body height and weight [a]	•	•									
Vital signs [b]	•	•	•	•	•	•	•	•	•	•	
B: HIV, HBV and HCV	•										
B/U: Hematology, clinical chemistry, urine analysis (safety panel)	•		•						•	•	
B: Pregnancy test	•	•							•	•	
U: Cotinine test	•	•									
U: Drug screen [c]	•	•									
Alcohol breath test	•	•									
P4M3 demonstration	•										
AE/SAE recording	•	•	•	•	•	•	•	•	•	•	•
Enrollment		•									
P4M3 product test [d]		•									
Randomization			•								
Informing subjects about study arm				•							
Collection of CIG butts for accountability			•	•	•	•	•	•			

E-liquid use (weight difference of Cartridges)				•	•	•	•	•			
B: BoExp in blood: COHb			•	•	•	•	•	•			
U: 24-h urine collection for BoExp (see table below)			•	•	•	•	•	•			
Intake of a caffeine tablet			•					•			
B: CYP1A2 activity			•					•			
FTND			•								
ABOUT–Product Experience			•	•	•	•	•	•			
HPT recording [e]				•	•	•	•	•			
P4M3 product events		•		•	•	•	•	•		•	

Abbreviations:

ABOUT = Assessment of behavioral outcomes related to tobacco and nicotine products; AE = Adverse event; B = Blood sample required; BMI = Body mass index; BoExp = Biomarker(s) of exposure; BoPH = Biomarker(s) of potential harm; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; FTND = Fagerström Tobacco and Nicotine Dependence; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = Human immunodeficiency virus; HPT = Human puffing topography; SA = smoking abstinence; SAE = Serious adverse event; U = Urine sample required. a) Height will be recorded only at screening.

b) Systolic and diastolic blood pressure, pulse rate, and respiratory rate.

c) Urine will be screened for the following drugs: amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates and methadone.

d) On Day -2 (admission), after inclusion/exclusion criteria are re-checked, eligible subjects will be enrolled and perform a product test using the 2 P4M3 flavor variants (CA35 and CM35). The site staff will provide them a training before on how to use the product. After the product test, subjects not willing to use P4M3 will be discontinued.

e) e) HPT recording on an ongoing basis for subjects in P4M3 arms.

f) Provided the 28-day Screening period has not exceeded, alternate subjects have to repeat the Admission visit Day -2of the following group to re-confirm their eligibility for randomization.

g) If a subject is discontinued from the study after enrollment, listed early termination procedures are performed unless the subject refuses to perform the assessments or is lost to follow-up.

h) Reporting of new AEs/SAEs by the subject and follow-up of ongoing AEs/SAEs by the site.
i) During the safety follow-up period, only medication taken for the treatment of AEs will be recorded.

Schedule of 24-hours Urine Collection Start

	Baseline	**Confinement Exposure Period**				
Study Day	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
BoExp and creatinine in 24-h urine	●	●	●	●	●	●
Bio-banking samples	●	●	●	●	●	●

Abbreviations:

BoExp = Biomarker(s) of exposure

13.2 FTND Scoring Manual

Scoring procedure (FTND_TS2.0 (AU2.0))

Test for Nicotine Dependence (UK-English)			
FTND Question		**Answer**	**Score**
1	How soon after you wake up do you smoke your first cigarette?	Within 5 minutes 6 to 30 minutes 31 to 60 minutes After 60 minutes	3 2 1 0
2	Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes No	1 0
3	Which cigarette would you hate most to give up?	The first one in the morning Any other	1 0
4	How many cigarettes per day do you smoke?	10 or less 11 to 20 21 to 30 31 or more	0 1 2 3
5	Do you smoke more frequently during the first hours after awakening than during the rest of the day?	Yes No	1 0

6	Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

The FTND total score is derived by summing the individual item scores if all items are non-missing, otherwise the total score is set to missing. For the FTND total score, descriptive statistics and frequency tables according to the following classification are provided (Fagerström et al. 2012):

Mild 0 – 3

Moderate 4 – 6

Severe 7 – 10

Signature Page for VV-TMF-04907 v2.0

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 25-Aug-2022 04:58:39 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 25-Aug-2022 07:08:30 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 25-Aug-2022 10:37:34 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 25-Aug-2022 13:03:46 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 25-Aug-2022 14:13:17 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 26-Aug-2022 10:35:51 GMT+0000

Signature Page for VV-TMF-04907 v2.0