PHILIP MORRIS PRODUCTS S.A.

Clinical Study Protocol

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
Short title:	Reduced HPHC exposure in cigarette smokers switching to P4M3 Gen. 2.0 compared to continuing smoking, or smoking abstinence
Product Name:	P4M3 Gen 2.0
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 3 2000 Neuchâtel, Switzerland
Version:	4.0, Approved
Date:	13 Apr 2022
Authors:	[redacted], PhD, Clinical Scientist [redacted], PhD, Study Statistician [redacted], MD, Medical Safety Officer

VERSION HISTORY

Version	Date	Protocol Update/Amendment
Original Document 1.0	07 Mar 2022	Not applicable
2.0	07 Mar 2022	Protocol Update
3.0	18 Mar 2022	Protocol Update
4.0	12 Apr 2022	Protocol Update

Synopsis

Sponsor:

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

Name of Product:

P4M3 Gen 2.0

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

Study Number:

P4-REXC-06-EU

Short Title:

Reduced HPHC exposure in cigarette smokers switching to P4M3 Gen. 2.0, compared to continuing smoking, or smoking abstinence

Primary Objective and Endpoints:

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.

Secondary Objectives:

Key secondary objectives

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 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.

Other secondary objectives

1. To monitor safety and tolerability in all subjects during the study.

Endpoints:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence 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 (Appendix D)
- Concomitant medications.

Exploratory Objectives

1. To determine the levels of BoExp given in Table 3 to selected HPHC 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. To determine the reductions of BoExp given in Table 1, Table 2, and Table 3 to selected HPHC in smokers quitting smoking compared to continuing CIG smoking or switching from CIG to P4M3 (CA35 and CM35 arms combined and separately) over 5 days.

3. To describe nicotine/tobacco product use in smokers switching from CIG to P4M3 (combined CA35 and CM35 arms; and CA35 and CM35 separately) compared to continuing CIG.

   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. To describe investigational product experience in smokers switching from CIG to P4M3 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. To describe Human Puffing Topography (HPT) over the entire exposure period in smokers switching to P4M3 (CA35 or CM35).

   Endpoints (Day 1 to Day 5):

   - Per-product use experience and per-day parameters (Appendix C)

6. To evaluate cytochrome P450 1A2 (CYP1A2) enzymatic activity in smokers switching to P4M3 (CA35 or CM35) and smoking abstinence compared to continued CIG smoking.

   Endpoints (Day -1 and Day 5):

   - Molar metabolic ratio of paraxanthine/caffeine in plasma

The estimands requested as per ICH guidelines [1] for all objectives are described in protocol statistical section.

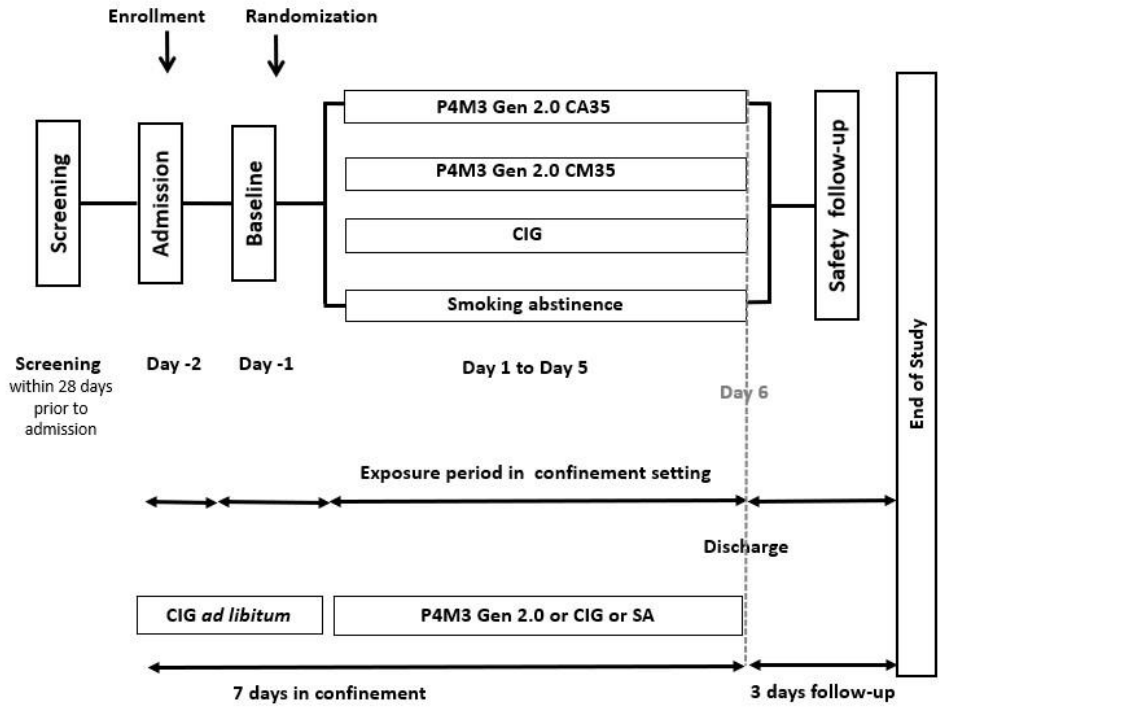
Study Hypothesis:

All the BoExp examined for the primary objective will demonstrate a reduction in subjects switching to P4M3 (subjects of CA35 and CM35 pooled together) compared to subjects continuing CIG.

Study Design:

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* study with unrestricted product use (P4M3 or CIG, in the respective arms) for a 5-day exposure period in the confinement setting (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 at Admission visit.

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

On Day -2 (Admission), after all selected inclusion/exclusion criteria have been verified, 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) 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 tobacco/nicotine containing product

(TNP) other than CIG (and P4M3 for the product test) will not be allowed after admission.

- 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). Baseline assessments will be performed as indicated in Appendix A.

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

- P4M3 Classic Auburn 3.5% nicotine (CA35) arm:
  18 subjects, *ad libitum* use of P4M3 using CA Cartridges
- P4M3 Classic Menthol 3.5% nicotine (CM35) arm:
  18 subjects, *ad libitum* use of P4M3 using CM Cartridges
- CIG smoker arm:
  18 subjects, *ad libitum* smoking of their own preferred CIG brand
- SA subject 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 on 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, use of P4M3 or CIG smoking in the respective arms 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.

The Exposure period to the assigned investigational product (IP) will end at 11:00 PM on Day 5, followed by Discharge on Day 6 after completion of all study procedures. Subjects may smoke CIG or use other TNP at their discretion after Discharge only.

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 any TNP at any time during the study (i.e., P4M3, CIGs) 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.

Biobanking:

If the subject consents, from the 24-hour urine collection, additional samples will be taken for long-term biobanking (two years at most) in view of further measurements of BoExp and stored at the bioanalytical laboratory (Appendix B).

Study Population and Main Criteria for Inclusion/Exclusion:

A sufficient number of healthy female and male smokers who meet all the following inclusion criteria will be enrolled into the study to ensure randomization of 72 subjects:

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	

Subjects who meet any of the following exclusion criteria will 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, 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	X	

of the Investigator would jeopardize the safety of the subject.		
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.*

Sample Size:

In this study, 72 healthy adult smokers will be randomized. This will provide more than 90% power to demonstrate a reduction for all BoExp tested in the primary objective in the combined P4M3 arms compared to the CIG arm, using a one-sided two-sample t-test with 2.5% type I error probability. This assumes, based on a previous similar study conducted by PMP (see ClinicalTrials.gov Identifier: NCT01959932), that the geometric mean ratio (GM) and the related geometric coefficient of variation (GCV) of the ratio between the combined P4M3 arms and the CIG arm are the following:

- GMR = 23.45% and GCV = 16.84% for COHb at Day 5,
- GMR = 41.63% and GCV = 26.10% for 3-HPMA at Day 5,
- GMR = 13.16% and GCV = 6.5% for 2-CyEMA at Day 5,
- GMR = 43.54% and GCV = 5.2% for Total NNAL at Day 5.

Investigational Products; Dose; and Mode of Administration:

Investigational Product:

P4M3 Battery Units and Cartridges will be provided by the Sponsor.

The following P4M3 variants will be investigated:

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

Comparator:

CIG arm: Subject's own preferred brand of commercially available, regular or mentholated CIG (not provided by the Sponsor).

Reference:

Not applicable.

Duration of Study:

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, followed by Discharge on Day 6), and a 3-day Safety follow-up period.

The End of the study (EOS) for a subject is defined as the completion of the 3-day Safety follow-up period either after the Discharge at Day 6, or after the early termination of the subject. The end of the whole study corresponds to the EOS of the last subject.

Statistical Methods:

Analysis Sets:

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.

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

Additional analysis sets may be defined in the SAP.

Statistical Analysis:

The primary objective will be analyzed using a linear mixed model for repeated measurements. A 1-sided pairwise comparison in the PPS between continuous smokers and smokers who switch to one of the P4M3 variants will be used to assess the primary study hypothesis.

The main comparison will be between the P4M3 arms (combined CA35 and CM35 arms) versus the CIG arm. Additional comparisons will be performed to compare each P4M3 arm against the CIG arm. Finally, comparisons between the other arms will be done as well (e.g., P4M3 arms combined and separately vs smoking abstinence; CIGs vs smoking abstinence).

Descriptive statistics will be presented at each timepoint, where applicable. Descriptive statistics will be presented for each arm separately as well as for the combined P4M3 variants (P4M3 CA35 + P4M3 CM35).

The other BoExp will be analyzed using a similar model to the primary analysis. Product use, HPT and questionnaires will be summarized using descriptive statistics.

Human Subject Protection and Independent Ethics Committee (IEC):

The study will follow the principles as defined in the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and in the Declaration of Helsinki and applicable regulation. Prior to the start of the study, the clinical study protocol, together with any other documents as required by the Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC.

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 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.

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Abbreviations and Definitions of Terms

Abbreviations

2-CyEMA	2-Cyanoethyl mercapturic acid *N*-Acetyl-*S*-(2-cyanoethyl)-L-cysteine
2-HPMA	2-hydroxypropylmercapturic acid
3-HMPMA	3-hydroxy-1-methylpropylmercapturic acid
3-HPMA	3-hydroxypropylmercapturic acid
3-OH-B[a]P	3-hydroxybenzo(a)pyrene
ABOUT	Assessment of behavioral outcomes related to tobacco and nicotine products
AE	Adverse event
BMI	Body mass index
BoExp	Biomarker of exposure
CA35	P4M3 Gen 2.0 variant Classic Auburn 3.5% nicotine
CAF	Caffeine
CI	Confidence interval
CIG	Conventional cigarette (smoking)
CM35	P4M3 Gen 2.0 variant Classic Menthol 3.5% nicotine
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTMS	Clinical trial management system
CV	Coefficient of variation
CYP1A2	Cytochrome P450 1A2
DHPMA	2,3-dihydroxypropylmercapturic acid
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
FEF	Forced expiratory flow

FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCV	Geometric coefficient of variation
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPHC(s)	Harmful and potentially harmful constituent(s)
HPT	Human puffing topography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IP	Investigational product
IEC	Independent Ethics Committee
IxRS	Interactive web/voice response system
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
MCEQ	Modified cigarette evaluation questionnaire
MDEDR	Miniaturized detachable external data recorder
MedDRA	Medical dictionary for regulatory activities
MHBMA	Monhydroxybutenyl mercapturic acid
NEQ	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NRT	Nicotine replacement therapy
PMP	Philip Morris Products S.A.
PP	Per protocol set
PI	Principal investigator
PX	Paraxanthine
QC	Quality control
SA	Smoking abstinence

SAE	Serious adverse event
SAP	Statistical analysis plan
SHM	Sample handling manual
SOP	Standard operating procedure
S-PMA	*S*-phenylmercapturic acid
TNP	Tobacco and/or nicotine containing product
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
vs	Versus
WHO	World Health Organization

Explanation of Terms

The following special terms are used in this protocol:

Alternate subjects	Subjects who have signed the ICF, have met the inclusion and exclusion criteria, and have been enrolled, but have not been randomized due to a sufficient number of subjects available for randomization at that time. In case the Admission Day-2 of the following group does not exceed the 28-day Screening period, to qualify for randomization, alternate subjects have to repeat the Admission visit to re-confirm their eligibility.
Cigarette(s) (CIG)	The term 'CIG' refers to commercially available regular or menthol cigarettes (manufactured) and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
Early termination	Premature termination of exposure to the Investigational Product after the start of the Exposure period in the confinement setting.
End of study (EOS)	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.
Randomization	Allocation of the respective product at any time on Day -1 utilizing an interactive web and voice response system (IxRS). On Day 1, the subjects will be individually informed about the product they are randomized to prior to the first product use.
Screening failure	All subjects that are not enrolled are considered as screen failures. Re-screening of subjects who did not meet any entry criteria will not be permitted.

1. Ethics and Regulations

1.1 Independent Ethics Committee (IEC) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] including the subject information sheet, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's brochure [IB], available safety information, curriculum vitae of the Principal Investigator(s) (PI(s)) and designee(s) and/or other evidence of qualifications and any other documents requested by an Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC. The IEC shall be appropriately constituted and perform its functions in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Good Clinical Practice (GCP) [2] and local requirements, as applicable.

In accordance with GCP, a written confirmation of the IEC approval should be provided to the Sponsor. This should identify the study (name of the PI(s) and designee(s), study number, and title) and the documents that have been approved by the IEC, with dates and version numbers, as well as the date of approval. The composition of the IEC, including the name and occupation of the chairperson, will be supplied to the Sponsor together with a GCP compliance statement.

The written approval from the IEC will be filed in the Principal Investigator file, and a copy will be filed in the study master file at the Sponsor or designated organization. The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC.

Any substantial change or addition to this protocol will require a written protocol amendment that must be approved by the Sponsor and the Principal Investigator(s). All amendments will be submitted to the IEC, and substantial amendments will only be implemented after approval by the IEC.

These requirements for approval should in no way prevent any action from being taken by the PI(s) or designee(s) or by the Sponsor to eliminate immediate hazards to the subjects. If such a change to the protocol is felt to be necessary by the PI(s) or designee(s), and is implemented for safety reasons, the Sponsor and the IEC should be informed immediately. The PI(s) is(are) responsible for local reporting (e.g., to the IEC) of serious adverse events (SAEs) that occur during the study, according to local regulations.

Relevant safety information will be submitted to the IEC during the study in accordance with national regulations and requirements.

Medically qualified study personnel will be available during the study.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [3] and are consistent with ICH/GCP [2] applicable regulatory principles.

The PI(s) or designee(s) agree(s) to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IEC. The PI(s) and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki will be filed in the Investigator's study file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

Before or at Screening Visit, the PI(s) or designee(s) will ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study, and the PI(s) or the designee(s) will answer all questions the subject might have to his/her full satisfaction. The subject will have sufficient time for consideration of his/her participation in the study and will be notified that he/she is free to withdraw his/her participation at any time.

Once the subject has received all the necessary information, and if he/she agrees to participate in the study, the subject and the person who conducted the informed consent discussion during Screening Visit will both sign, date, and time the ICF. The ICF includes both the subject information sheet and informed consent. No study-specific procedures will be performed before the ICF has been signed (including date and time).

In addition to consenting to study participation, the subject will be asked for their consent to the storage of urine samples for long-term biobanking (two years at most), i.e., the storage of samples from the 24-hour urine collection at the bioanalytical laboratory (Appendix B), in view of further measurements of BoExp. These analyses are not described in the protocol or statistical analysis plan (SAP) and will not be included in the clinical study report (CSR), but in a separate report. Any additional analysis performed will also be covered by data confidentiality, as it is for the main analysis described in this protocol.

The subject's consent to urine sample biobanking is not a requirement for the study participation and the subject's participation in the study does not depend on their consenting to biobanking.

The original dated and signed ICF(s) must be kept by the PI(s) and filed in the Principal Investigator's file at the site or with the subject's files and a copy must be given to the subject.

The subject will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed unless he/she disagrees. The subject will be informed that additional data analysis not mentioned in the protocol or in the statistical analysis plan (SAP) might be performed with the collected data at any later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.3.2 Amendment to the Informed Consent Form

If a protocol amendment is required, or if any new information regarding the risk profile of the investigational product (IP) becomes available for any other reason deemed necessary, an amendment to the ICF may be required. If a revision of the ICF is necessary, the PI(s) or designee will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IEC before subjects are required to re-sign the ICF (including date and time). If new and important safety information is received, subjects who already completed or are discontinued from the study will be informed by letter, email, or phone call.

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, PI(s) or designee(s) abide by the principles of the ICH guidelines on GCP [2]. These guidelines apply specifically to pharmaceutical development, but nevertheless provide a robust and ethical framework for conducting clinical studies with products such as P4M3 Gen 2.0. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki [3].

2 Introduction

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette (CIG) smoking causes pulmonary, cardiovascular and other serious diseases in smokers [4] due to the exposure of toxicants in the CIG smoke, i.e., its harmful and potentially harmful constituents (HPHC). There is no safe CIG smoking, and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers decide to continue smoking. The development of novel tobacco and nicotine containing products (TNP) with the potential to be less harmful than CIG represent an approach to reduce CIG-related deaths and diseases among smokers switching to ENDS who would have otherwise continued smoking [5].

Philip Morris Products S.A. (PMP) is developing such alternative products that have the potential to reduce individual risk and population harm in comparison to smoking CIG. These products aim to substantially reduce or eliminate the exposure to HPHC generated from CIG smoke except nicotine, while providing an acceptable substitute for CIG smoking and lowering the health risk.

One of these products is P4M3 Gen 2.0 (P4M3), which is an electronic nicotine delivery system (ENDS) or electronic cigarette (e-cigarette). The liquid used in P4M3 is composed of propylene glycol, vegetable glycerol, water, nicotine, lactic acid, benzoic acid, and flavors.

E-cigarettes have the potential to benefit adult smokers who are not pregnant if used as a complete substitute for combustible tobacco containing products such as CIG. However, in some specific conditions of e-cigarette use, harm has been recently reported. In a recent investigation, the Centers for Disease Control and Prevention (CDC) have analyzed national data on e-cigarette, or vaping, product use-associated lung injury. CDC and FDA recommend that people should not use Tetrahydrocannabinol (THC)-containing e-cigarette or vaping products, particularly from informal sources like friends, family, or in-person or online sellers. Vitamin E acetate should not be added to e-cigarette or vaping products, or any other substances not intended by the manufacturer.

CDC, FDA, and state health authorities have made progress in identifying substances of concern in e-cigarettes or vaping products. However, there are many different substances and product sources that remain under investigation, and there may be more than one cause.

Given that context, when developing new products such as P4M3, appropriate assessment including comprehensive understanding of product characterization, its safety, and related impact of product use in humans is critical. P4M3 is a closed e-cigarette with a Cartridge that cannot be refilled and for which the e-liquid does not contain THC or Vitamin E acetate (section 2.1.2).

2.1.2 Description of the Product and Scientific Findings

P4M3 Gen 2.0 is an Electronic Nicotine Delivery System (ENDS) that produces an aerosol through vaporization of an e-liquid. The e-liquid is composed of propylene glycol, vegetable glycerol, water, nicotine, lactic acid, benzoic acid, and flavors. P4M3 is a closed e-cigarette composed of a Battery Unit containing all the electronics with a rechargeable battery and a disposable, replaceable Cartridge containing the e-liquid and the heating element. The P4M3 Cartridge is not refillable.

The aerosol production (heating cycle) is triggered by a pressure sensor in the Battery Unit when a puff is detected. The e-liquid aerosol is produced by a heater composed of a fine mesh of stainless-steel wires heated by an electric current.

The aerosol generated by P4M3 is free from the majority of HPHC associated with heating or burning tobacco, except nicotine. P4M3 does not contain tobacco and there is no combustion during use.

The non-clinical assessment of P4M3 is described in the Investigator's Brochure [6] and supports the clinical assessment of P4M3. P4M3 will also be tested in a pharmacokinetic study in humans; this study has been submitted.

In 2016, FDA finalized a rule extending its Center for Tobacco products' (CTP's) regulatory authority to cover all tobacco products, including ENDS that meet the definition of a tobacco product. FDA regulates the manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of ENDS, including components and parts of ENDS.

When assessing ENDS use, significant inter-subject variability has been described for human puffing topography (HPT) parameters, especially puff duration, puff frequency, and flow rate [7]. Experienced e-cigarette users may extract more nicotine by puffing with a low flow rate and long duration puffs in comparison to CIG smokers. E-cigarette design features also affect nicotine exposure; increasing the battery voltage output and e-liquid nicotine concentration increases the nicotine delivery [8]. Differences in puffing behavior (such as puff duration or depth of inhalation) resulted in a faster absorption rate and a higher amount of nicotine absorption in experienced e-cigarette users as compared to naïve e-cigarette users when using the same e-cigarette [9]. Battery output, type of wicks, ventilation holes, and other mechanical characteristics of each individual e-cigarette

product determine how much aerosol and nicotine is released. More effective and appealing e-cigarette products to provide satisfying alternatives to smoking has led to e-liquids containing "nicotine salts". Nicotine salts are formed by the reaction of nicotine with a suitable acid and are less volatile than freebase nicotine [10]. As a result, a greater fraction of the nicotine in the salt form is expected to remain in inhaled aerosol droplets until the aerosol reaches the alveoli for pulmonary absorption.

2.2 Purpose of the Study

The overall goal of the study is to demonstrate reduction in the levels of Biomarkers of Exposure (BoExp) to selected HPHC and to obtain safety information in healthy subjects switching from CIG to P4M3 as compared to smoking abstinence (SA), or to smokers continuing smoking CIG in a confinement setting for 5 days.

Product use patterns, puffing behavior and overall exposure to nicotine from two P4M3 variants, CA35 and CM35, will also be assessed.

Information on changes in investigational product experience upon switching to P4M3 will be provided by measuring self-reported behavioral outcomes, compared to CIG smoking.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Information on health risks associated with smoking and smoking cessation advice will be provided at the Screening Visit, Admission Visit, and at Discharge on Day 6, respectively. The advice will follow the recommendations of the World Health Organization (WHO) "Evidence based Recommendations on the Treatment of Tobacco Dependence" [11]. Subjects who are motivated to quit smoking during the study will be encouraged to do so and will be referred to appropriate medical services for necessary support and counselling. Subjects who participate in this study will also benefit from repeated and detailed health check-ups.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

The risk of scheduled procedures in the present study (e.g., blood samples) are deemed to be on par with procedures routinely performed during normal or extended health examinations by the subject's healthcare professional. The total volume of blood to be drawn is approximately 81 mL and does not exceed the levels for a standard blood donation. The risks related to blood sampling include for example: excessive bleeding, fainting, hematoma, paresthesia, or infection, and those related to the total amount of blood taken over a time span such as weakness, dizziness, or anemia.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product

By product design, the aerosol generated by P4M3 Gen 2.0 is free from the majority of HPHC associated with heating or burning tobacco, except nicotine. However, given the current state of knowledge about the product, it has not yet been demonstrated that P4M3 or other e-cigarettes reduce the risk of developing smoking-related diseases compared to CIG.

Due to sensorial and technological differences between P4M3 and CIG, it is possible that subjects will adapt their behavior, e.g., by modifying the number, the volume and/or duration of puffs, as well as the intensity of inhalation.

The confinement setting may also have an influence on puffing behavior and nicotine uptake.

An adult smoker using P4M3 may experience:

- Transient nicotine withdrawal symptoms (e.g., urge to smoke, irritability, anxiety feelings, restlessness, and difficulty to concentrate) similar to cravings observed during smoking cessation
- Transient symptoms suggesting mild nicotine overdose such as stimulatory effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, and decreased ability to concentrate), gastric acid secretion, and vomiting. Individuals who experience adverse events (AEs) (suggesting excessive stimulant effects) should be instructed to reduce their intensity of product use by decreasing the number of puffs and/or the intensity of puffing
- Change in smoking habits due to study requirements and related concomitant symptoms, e.g., craving.

Support during periods of abstinence from any tobacco and nicotine containing products will be provided (see section 7.3).

Further risk mitigation will include:

- Using commonly accepted research and scientific standards (e.g., blood samples not to exceed blood donation standards)
- Medical supervision of all study subjects with follow-up of those who have experienced AEs/serious adverse events (SAEs)

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained in detail to study participants. Unexpected malfunction of the P4M3 device may lead to unforeseeable risk. Risk mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 Study Objectives

The estimands requested as per ICH guidelines [1] for all objectives are listed in section 12.5 for the primary objective, section 12.6 for secondary objectives, and section 12.7 for exploratory objectives.

3.1 Primary Objective

The primary objective of this study is:

1. To demonstrate the reduction of BoExp to selected HPHC given in Table 4 in smokers switching from CIG to P4M3 (combined CA35 and CM35 arms) compared to continuing CIG smoking for 5 days.

Table 4 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 12.3).

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 to selected HPHC given in Table 5 in smokers switching from CIG to P4M3 (combined CA35 and CM35 arms) compared to continuing CIG smoking for 5 days.

Table 5 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 expressed as concentration adjusted for creatinine in 24-hour urine.*

2. To demonstrate the reduction of BoExp to selected HPHC given in Table 4 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 5 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 4 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 5 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 12.3).

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 section 12.6.1).

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 (Appendix D)
- Concomitant medications.

3.3 Exploratory Objectives

3.3.1 Exploratory Objective 1 and Endpoints

The exploratory objective 1 of this study is to determine the levels of BoExp to selected HPHC given in Table 6 in smokers switching from CIG to P4M3 (CA35 and CM35 arms combined and separately) compared to continuing CIG smoking for 5 days.

Table 6 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.

3.3.2 Exploratory Objective 2 and Endpoints

The exploratory objective 2 of this study is to determine the reductions of BoExp to selected HPHC given in Table 4, Table 5, and Table 6 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.

3.3.3 Exploratory Objective 3 and Endpoints

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 use.

3.3.4 Exploratory Objective 4 and Endpoints

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) (assessed only in subjects randomized to P4M3 or CIG)

3.3.5 Exploratory Objective 5 and Endpoints

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 (Appendix C).

3.3.6 Exploratory Objective 6 and Endpoints

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)

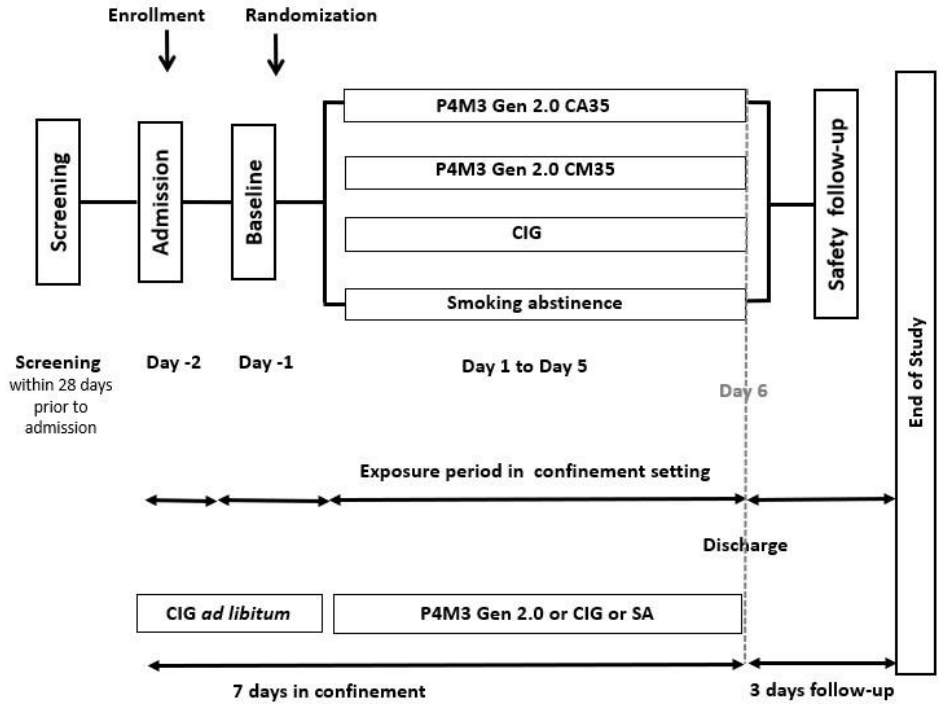
- Molar metabolic ratio of paraxanthine/caffeine in plasma.

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 2).



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

Figure 2 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). Baseline assessments will be performed as indicated in Appendix A.

  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 AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs ongoing at Discharge will be conducted by the investigational site.

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.

HPHC considered to be of health concern have been reported by different regulatory bodies and health organizations [12, 13]. 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" [14]. More recently, a guidance was issued by the FDA on which HPHC to be considered for reporting in e-liquids or aerosols of ENDS [15].

[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.

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) [13]
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 [16]), 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.

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).

5.1 Selection of Study Population

5.1.1 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	

5.1.2 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.*

5.2 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, 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.

5.3 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.

5.4 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.

6 Investigational Products

6.1 Description of Investigational Products

P4M3 Gen 2.0 will be provided by the Sponsor.

The distribution, dispensation and return of investigational products will be controlled by qualified and appropriately trained investigational site staff.

6.1.1 Test Product

P4M3 Gen 2.0 is an ENDS or electronic cigarette (e-cigarette), which produces an aerosol through vaporization of an e-liquid. P4M3 Gen 2.0 is composed of a Battery Unit containing all the control electronics with the rechargeable battery and a disposable Cartridge containing the e-liquid and the heating element. The Battery Unit comprises several functions. The Battery Unit provides electrical power when required, which is activated by puff detection. The Battery Unit enables two power settings for adjusting the volume of the aerosol cloud, i.e., regular (5.5 Watts) or low (4.5 Watts) power setting. The device has a "dry mesh detection" function to prevent overheating when the liquid on heater is not sufficient.

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

The Battery Unit is controlled through a single multi-function button used for switching on and off and allowing the modification of both the haptic (vibration) and the power level (regular or low).

The Cartridge consists of a reservoir for storing the e-liquid, which also acts as the mouthpiece and includes the air flow channels to carry the aerosol from the heater to the user. The Cartridge contains the e-liquid, the mesh heater sub-assembly and the porous materials for liquid retention and transport from the reservoir to the heater. The Cartridge is disposed of when the e-liquid in the reservoir is depleted.

The P4M3 Gen 2.0 e-liquid formulations are composed of propylene glycol, vegetable glycerin, water, tobacco-derived nicotine, lactic acid, benzoic acid and could differ in flavors and nicotine concentrations. The following P4M3 Gen 2.0 e-liquid formulations (variants) will be investigated in this study (Table 7).

Table 7 P4M3 Gen 2.0 variants

Name	Name in the study	Nicotine concentration	e-liquid flavor

P4M3 Gen 2.0 Classic Auburn	CA35	3.5 %	Tobacco
P4M3 Gen 2.0 Classic Menthol	CM35	3.5 %	Menthol

The non-clinical assessment is described in the Investigator's brochure and supports the clinical assessment of P4M3 Gen 2.0.

6.1.2 Reference Product / Baseline Product

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

All eligible subjects will be asked to purchase their usual brand of CIG prior to Admission (Day -2). Every subject needs to bring a sufficient number of unopened, single-brand packs of CIGs for the entire confinement period which will be kept in secured storage room at site with access limited to authorized personnel only

6.1.3 Packaging and Labeling

At Admission (Day -2), all study subjects will provide a sufficient number of sealed packs of CIGs to the investigational site staff. The CIG pack provided by the subject should not be opened and the cellophane should be intact.

Each pack of CIGs provided by the subject will be labeled to identify to which subject the CIGs belong to. The investigational site staff will return all unused products to the subjects at Discharge or Early termination.

For P4M3, packs of P4M3 Cartridges will be printed with the necessary information including, but not limited to, product code and expiry date.

6.2 Use of Investigational Product(s)

Subjects will not be forced to smoke CIGs or use P4M3 and will be free to stop smoking CIG/using P4M3 at any time of the study.

During the screening period, subjects will be allowed to smoke and use tobacco/nicotine-containing products according to their product use habits except during the procedures of the Screening Visit (section 9.1).

6.2.1 Admission Day (Day -2 to Day -1)

After enrolment in the study, subjects will be provided with information on the risks of smoking, advice on smoking cessation, and will be briefed on P4M3 (see section 7.2). They will be informed on the use of P4M3, including how to switch the power setting, and will perform a product test with P4M3 with an *ad libitum* use regimen for a duration of approximately 10 minutes 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 and during assessments requiring smoking breaks. Use of any TNP other than CIG and P4M3 will not be allowed after admission.

6.2.2 Baseline Period (Day -1 to Day 1)

All subjects may continue smoking their CIG *ad libitum,* except before and during assessments requiring smoking breaks.

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

- P4M3 Classic Auburn 3.5% nicotine (CA35) arm; *ad libitum* use of P4M3 using CA35 Cartridges
- P4M3 Classic Menthol 3.5% nicotine (CM35) arm; *ad libitum* use of P4M3 using CM35 Cartridges
- CIG smoker arm; *ad libitum* use of subject's own preferred CIG brand
- SA arm; subject will abstain from CIG smoking

6.2.3 Exposure Period (Day 1 to Day 5)

The Exposure period in confinement consists of 5 days of *ad libitum* use of the assigned product in the P4M3 and CIG arms. Except during study procedures, subjects can use P4M3 or consume CIG, and select the power setting (P4M3 only). Site staff will distribute assigned products to the subject and record all products distributed in the source documentation. 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. The exposure period to the assigned investigational product (IP) will end at Day 5, 11:00 PM, after which subjects will be asked to remain abstinent of any use of TNP until the end of their 24-hour urine collection and completion of study procedures on Day 6.

6.2.4 Day of Discharge (Day 6)

Following the completion of study procedures (including receiving information on the risks of smoking and smoking cessation advice), subjects will be discharged from confinement. Subjects may smoke CIG or use other TNP at their discretion after Discharge.

6.2.5 Safety Follow-up Period

During the 3-day safety follow-up period, subjects will be free to use any TNP according to their usual habits.

6.2.6 Stopping Rules for Investigational Product

For safety purposes, using P4M3 or smoking CIG should be temporarily stopped in the event of any signs suggesting nicotine overexposure, e.g., gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach pains, or abdominal pain), cold sweats, headache, dizziness and breathing problems, or any reasons at the discretion of the Investigator.

For subjects who are discontinued, the reason for discontinuation should be documented in the source documents and in the CRF and subjects will undertake early termination procedures (section 9.5), unless they disagree, or certain procedures have already been performed.

6.3 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.

6.4 Blinding

This is an open-label study; hence the subjects and PI(s) or designees will be unblinded to the subject's arm.

6.5 Investigational Product Accountability and Compliance

6.5.1 Dispensing Investigational Product

CIGs for consumption during the confinement period, i.e., on Day -1 to end of Exposure period on Day 5 11:00 PM, will be dispensed by the investigational site staff as per the study design.

P4M3 for use at the product test on Admission Day -2, and from Day 1 onwards to end of Exposure period on Day 5 11:00 PM, comprising of a fully charged Battery Unit with a full Cartridge, will be dispensed by the investigational site staff, as per the study design.

On each day of the confinement period, the time of dispense and return for each product (CIG/ P4M3) use will be documented from Day -1 until end of Exposure period on Day 5 11:00 PM.

On the Discharge on Day 6, subjects who wish to smoke CIG or other TNPs will be allowed to do so only after the end of 24-hour urine collection, and after completion of all study procedures.

P4M3 will not be promoted for commercial distribution or test market.

6.5.2 Storage and Accountability

P4M3 and CIG will be stored in a secured storage location at site with access limited to authorized personnel only. The study collaborator designated by the PI will be responsible for the storage and accountability of the IPs in accordance with Sponsor's requirements. P4M3 Battery Units and Cartridges must be stored under controlled conditions (temperature ≥5° C, ≤30° C; humidity <70%), whereas CIG can be stored in normal conditions (at ambient temperature with no temperature control).

During the confinement period, subjects will return each used P4M3 Cartridge, or butt (immediately after smoking) of each used CIG to the site collaborators for accountability. The time of return of the products will be documented in an appropriate log.

6.5.3 Investigational Product Retention

Used and unused P4M3 Battery Units and P4M3 Cartridges will be returned to the Sponsor or disposed as per Sponsor instruction upon study completion. Smoked CIG butts will be disposed upon study completion once accountability is completed adequately.

6.5.4 Compliance to Investigational and Reference Products

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/CIG butts by designated investigational site staff. Distribution and return of these products will be documented in appropriate logs.

6.6 Restrictions

6.6.1 Smoking Restrictions

During the Screening period, subjects will be allowed to use any nicotine/tobacco-containing products according to their usual habits except during the procedures of the Screening Visit (section 9.1.1). Spirometry assessments at Screening and at Day -1 will be performed at least 1 hour after stopping smoking (section 9.1.1 and 9.2.2).

From Admission (Day -1) to Discharge (Day 6) or Early termination, use of any nicotine/tobacco containing products, except use as per study design of the allocated product, will not be permitted.

To avoid cross smoke contamination between the four study arms during confinement period, subjects must use their assigned product (P4M3 or CIG) in separate smoking rooms.

Using P4M3 or smoking CIG will not be allowed during study procedures.

6.6.2 Dietary Restrictions

A standard diet will be designed by a dietician for the whole confinement period. For each meal, the caloric and fat content should be controlled to avoid a “high-fat” diet. A “high-fat” diet is defined as a diet which contains “approximately 50 percent of total caloric content of the meal [from fat] and is high in calories (approximately 800 to 1000 calories)” [17].

To avoid any effect on assessment of biomarkers of exposure, grilled or pan-fried meat, pre-cooked meats (e.g., tuna, ham, corned beef, and smoked meats), bacon and sausage will not be permitted. In addition, alcohol, broccoli, brussels sprouts, cauliflower, grapefruit and xanthine-containing foods and beverages (coffee, tea, chocolate, cocoa, mate, guarana, etc.) will not be allowed except when the subject will be asked to take a caffeine tablet for one of the assessments of CYP1A2.

Subjects will not be allowed to bring their own food (including sweets or chewing gum, etc.) or beverages to the investigational site. Meals will be served according to the agreed schedules. Additional light snacks, fruits (except grapefruits), and raw vegetables can be distributed to the subjects without restrictions at any time during confinement if they comply with the dietician’s standard diet. Consumption of non-carbonated water is

allowed. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed during the study. The same menu and meal schedule will be administered uniformly for all subjects in all study arms.

A fasting state will be observed for at least 6 hours prior to blood drawings for:

- Safety laboratory on Day -1 and Day 6.

6.7 Concomitant Medication

All medication taken within 4 weeks prior to the ICF signature will be considered prior medication. All medication taken from Screening visit to end of the Safety follow-up period will be considered concomitant medication.

Medications will be allowed and carefully monitored during the study by the Investigator or designee. The Investigator or designee is responsible for the medical care including medication of the subjects during their participation in the study. Any decisions regarding the prescription of medication will be taken in the best interest of the subject. The use of any concomitant medication must be fully documented in the source document and transcribed into the CRF.

7 Study Procedures

Personnel performing study assessments must have the appropriate and fully documented training. An overview of all study assessments is shown in the schedule of events (see Appendix A). In this section, only the expected/planned timepoints for the various assessments are described. Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care. Site personnel will adhere to the site's standard operating procedures (SOPs) for study related procedures.

7.1 Informed Consent

Prior to any study assessment being performed, the subject will be asked to provide his/her written consent to participate to the study (ICF for study participation) (section 9.1.1). All the assessments must start after the time of ICF signature by the subject for study participation.

In addition to the consent for study participation, the subject will be asked to provide her/his optional consent for biobanking (see section 1.3.1). The subject's participation in the study does not depend on the optional consent.

All consents will be captured in the eCRF.

7.2 Information on the Risk of Smoking and Smoking Cessation Advice and Briefing

At the Screening visit, before enrollment at Day -2 and at Discharge on Day 6, each subject will be given during the same session i) information on the risks of smoking, ii) smoking cessation advice, and iii) briefing on P4M3.

The information on the risk of smoking and the advice on smoking cessation will take the form of a brief interview according to the WHO recommendations and of the Public Health Service [18, 19]. The briefing of subjects on P4M3 will address any intended or unintended beliefs that participants may have about P4M3. The goal of the briefing is to help ensure that subjects enter and exit the study with an accurate understanding of the product risks, including an understanding that ENDS have not been demonstrated to be less harmful than CIG.

Details of the sessions will be recorded in the source document file. These sessions will be given to the subjects on an individual basis during a face-to-face meeting between the subject and the PI(s) or designee(s) and may additionally be given in a group session.

7.3 Support during Abstinence from any Tobacco and Nicotine Containing Products

Subjects will be offered support during periods of abstinence from any TNP during the study by the Investigator and/or investigational site staff. Support resources will include counselling and assistance, entertainment, monitoring of the subject's behavior, and AEs.

7.4 Clinical and Other Assessments

The results of the clinical assessments described in this section will be recorded in the CRF.

Any clinically relevant medical condition detected during Screening visit assessments has to be documented as a concomitant disease. This also applies to clinically relevant findings in laboratory values, vital signs, spirometry, and ECGs detected during Screening visit assessments. Any untoward medical occurrence in a subject detected during the study which was not present at Screening visit must be documented as an AE. Worsening of a pre-existing condition from Screening visit onwards will also be documented as an AE.

7.4.1 Demographic Data

Sex, date of birth, and race will be recorded.

7.4.2 Medical History, Concomitant Disease, Previous and Concomitant Medications

Relevant medical history or any concomitant disease will be documented at the Screening visit. Medical history is defined as any condition that started and ended prior to the ICF signature at the Screening visit. A concomitant disease is defined as any condition that is either detected or is still ongoing at the time of ICF signature. The final status of any concomitant disease (i.e., stop date or ongoing) should be verified at each visit.

Prior medication taken within 4 weeks prior to the Screening visit and any concomitant medication will be documented. Any medication started prior to the Screening visit and still being taken by the subject will be considered concomitant medication. Medication initiated after the Screening visit will also be referred to as concomitant medication. The definition of concomitant medication applies to both prescribed and over-the-counter products.

Records of medication taken should include the drug name (preferably both generic and trade name), route of administration (e.g., oral, intravenous), dose and frequency (expressed in metric units, e.g., mg, mL, or IU), indication, and the start and, if applicable, the stop date (day, month, and year). Therapy changes (including changes of regimen) during the

study will be documented. If a concomitant medication is still being taken by the subject at the end of the study, this will be recorded in the CRF.

7.4.3 Physical Examination

A physical examination will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, thyroid gland, chest, lungs, back, abdomen, dentition, gastrointestinal, cardiovascular, musculosceletal and neurological systems. The physical examination is to be conducted by the Investigator or designated fully trained representative.

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

7.4.4 Body Height and Weight

Body weight and height will be recorded at the Screening Visit, body weight will also be recorded at Admission Visit Day -2.

The BMI will be calculated from the body weight and height using the following formula:

$$\text{BMI} = \frac{\text{weight in kilograms}}{\text{height in meters}^2} = \frac{kg}{m^2}$$

The BMI will be used to assess eligibility for enrolment.

7.4.5 Vital Signs

Vital signs will include systolic and diastolic blood pressure, respiratory rate and pulse rate.

All parameters will be recorded in supine position after the subject has rested for at least 5 minutes. Subjects should have abstained from using any TNP for at least 15 minutes prior to Vital signs assessment.

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

7.4.6 Spirometry

Spirometry will be performed at the Screening visit, at Baseline visit Day -1, and at Discharge (Day 6), or Early termination, in accordance with the 2019 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry [20, 21]. Spirometry predicted values will be

standardized to the National Health and Nutrition Examination Survey III predicted set [22].

Assessed parameters will include: FEV_1, FEV_1 % predicted, FVC, FVC % predicted and FEV_1/FVC.

All personnel performing spirometry testing should have the appropriate training and quality control measures should be put into place and be properly documented. The testing will be performed in sitting position at rest for at least 15 minutes and at least 1 hour after smoking CIG (Screening visit).

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

Any printouts of Spirometry on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents.

7.4.7 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

All ECGs will be reviewed on an ongoing basis by the Investigator or designee. The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected according to Fridericia's formula.

For those results outside of the normal range, the Investigator will determine appropriate follow-up including reporting of any AEs.

Any printouts of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents.

7.4.8 Biomarker Assessment

All bioanalytical assays and laboratory assessments will be carried out using validated methods (sections 7.5 and 7.6). The bioanalytical methods used will be documented in the respective bioanalytical plans/reports. A list of laboratories is provided in Appendix B.

Blood samples and 24-hours urine samples will be collected according to the assessment schedule (Appendix A) to measure Biomarkers of Exposure to nicotine and some HPHC:

- In blood: carboxyhemoglobin (% of saturation of hemoglobin)
- In 24-hours urine: 3-HPMA, 2CyEMA, NNAL, S-PMA, 3-HMPMA, total NNN, 2-HPMA, 3-OH-B[a]P, DHPMA, NEQ, Cd, Cr, Pb, and Ni (creatinine normalization)

7.4.9 Laboratory Assessments

Clinical Chemistry, Hematology, and Urine Analysis for Safety Panel

Subjects should have fasted for at least 6 hours prior to hematology and clinical chemistry analyses, except at Screening visit and Early termination where non-fasting samples can be used. Tests will be conducted at a local laboratory (see Appendix B). If during the screening period a blood sample is not suitable for analysis (e.g., blood clotting) a re-test should be performed for the specific parameters which are not available. Safety urine analysis will be also assessed.

Parameters to be tested are listed in (Appendix D).

Serology

At the Screening visit, tests for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (anti-HIV1/2) will be performed.

CYP1A2

CYP1A2 activity will be assessed in plasma by measuring paraxanthine (PX) and caffeine (CAF) concentrations and calculating the PX/CAF molar metabolic ratio [23] on Baseline Day -1 and Day 5. Samples to measure PX and CAF will be drawn approximately 6 hours (±15 minutes) after the intake a caffeine tablet (approx. 200 mg caffeine). The exact time of intake of caffeine tablet in the morning and of the time of blood sampling must be recorded.

Urine Drug Screening

At Screening visit and on Admission Day -2, a urine drug screen will be performed. The urine will be screened for amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

In case of a positive urine drug test, a re-test will not be allowed to evaluate eligibility. In case of an inconclusive test, a re-test can be performed but this needs to be done immediately after the inconclusive test.

Urine Cotinine Screening

A urine cotinine test will be performed to confirm the nicotine/tobacco use status.

The test must detect cotinine with a threshold of ≥ 200 ng/mL. In case of a negative cotinine test, a re-test will not be allowed to evaluate eligibility. In case of an inconclusive test, a re-test can be performed but this needs to be done immediately after the inconclusive test.

Alcohol Test

An alcohol breath test will be performed.

Serum Pregnancy Test

A serum pregnancy test will be performed for all female subjects. Subjects with a positive pregnancy test or unclear results (from one repetition) before product testing and enrolment will be considered as screen failures. In case of any positive pregnancy test, the Investigator or designee will inform the subject about the risks associated with smoking during pregnancy and subjects will be referred to health care facility/health care provider for pregnancy follow-up.

All pregnancies detected during the study must be reported and handled as described in section 8.5.

7.4.10 Sample Handling, Storage, and Shipment

Urine drug tests and urine cotinine tests, as well as all safety panel tests and pregnancy tests, will be done by the site personnel at the site. All other blood and urine samples will be managed by the laboratory designated in Appendix B.

Detailed procedures for handling of samples will be described in the sample handling manual (SHM). Safety laboratory samples will be destroyed as per laboratory local regulations. All other samples (except biobanking samples) will be destroyed after the Clinical Study Report (CSR) has been finalized. The facilities at which the samples are stored will be informed in writing by the Sponsor when destruction of the samples shall be performed.

Blood Samples

Blood samples will be drawn by qualified and trained site personnel and according to the standard operating procedures (SOPs) at the investigational site.
Since the test for nicotine concentration is highly sensitive, precautions should be taken during blood sampling and processing to prevent the contamination of samples with environmental nicotine.

In total, approximately 81 mL of blood will be collected for this study including samples for determination of CYP1A2 activity (10 mL), COHb (30 mL) and safety laboratory (approximately 40.5 mL). This calculation is based on an individual volume of each sample of 5 mL for CYP1A2 analysis, 13.5 mL per safety laboratory assessments (including serology and pregnancy test), and 5 mL for COHb assessment. The total volume of blood drawn (approximately 81 mL) will not exceed the levels for a standard blood donation.

Details on the procedures for collection, labelling, processing, and shipment of samples will be described in the SHM.

Urine Samples

Spot urine samples will be used for the urine drug screen, urine cotinine screen, and safety urine analysis at Screening visit and Baseline visit on Day -1, and after completion of 24-hour urine sample collection on Day 6.

24-hour urine collection Subjects will discard their first void in the morning of Day -1. The collection period will start immediately after. After 24-hours ±1h of urine collection, subjects will empty their bladder again in the morning of the visit and this urine will be used as the final portion of the 24-hour urine sample.

During the collection period, all urine passed must be collected in the sampling container. No urine should be passed into the toilet. The start and the end time of urine collection will be recorded by the subject and checked by the site staff. The volume of 24-hour urine will be measured by the site staff upon collection of urine containers from the subjects. For assessment of urine BoExp, creatinine aliquots from the 24-hour urine collection will be taken. In the schedule of events for the 24-hour urine collection, the dot corresponds to the day on which the 24-hour urine collection period starts.

Biobanking of urine If a subject gives additional consent for biobanking, additional samples of urine from the 24-hour collection will be collected, i.e., from the daily collections commencing Day -1, 1, 2, 3, 4, and 5. The samples intended for biobanking will be kept frozen and will be shipped to a central storage facility according to the SHM. After the final CSR is signed, samples of urine will be stored for a maximum duration of 2 years.

7.5 Other Study Procedures

7.5.1 Demonstration P4M3 and Product Test

All subjects will have a demonstration of P4M3 by the investigational site staff at the Screening visit without product use.

At Admission (Day -2), after enrolment, investigational site staff will inform subjects on product use and subjects will have a product test with P4M3 *ad libitum* for a duration of approximately 10 minutes per flavor.

7.5.2 Human Puffing Topography Assessment

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

The miniaturized detachable external data recorder (MDEDR) puffing topography device measures and records the flow rate, other per-puff parameters, and power setting of P4M3 as listed in Appendix C. From the per-puff measurements, per-day parameters will be derived.

The MDEDR puffing topography device will be used with the P4M3 on Day 1 to Day 5 with data recording during *ad libitum* use. Data will not be collected during CIG smoking.

The P4M3 is equipped with a pressure sensor, which measures the pressure at the Cartridge level. When a puff is drawn, the P4M3 calculates the difference of pressure between the atmospheric pressure and the pressure measured at the Cartridge level. The aerosol production (heating cycle) is then triggered based on the difference of pressure values calculated by the P4M3. The MDEDR puffing topography device allows to collect these data when it is mechanically attached to the Battery Unit of P4M3 and electronically connected to its USB port. The MDEDR puffing topography device works as a data logger. Once connected to the P4M3, the MDEDR puffing topography device will record HPT data. Any malfunction of the MDEDR puffing topography device will be documented in the appropriate log.

One MDEDR puffing topography device will be assigned at Day -1 for each subject and will be used for all further HPT assessments. A replacement device will be provided in case of malfunction of the device assigned. The Sponsor will provide training on the use of the MDEDR puffing topography device to the investigational site staff which will be responsible for the HPT assessment. All MDEDR puffing topography devices will be returned to the Sponsor after completion of the study.

Prior to calculation of the parameters, the Sponsor's HPT group will process, validate, and discard any invalid data, as per the Sponsor's SOPs. The Sponsor will provide copies of both the raw and validated HPT datasets to the Investigator. Only valid data will be part of the study database and will be analyzed.

7.5.3 Weighing of P4M3 Cartridge

P4M3 Cartridges will be weighed by the study personnel before and after daily product use by the subjects to estimate the amount of liquid used, to calculate delivered nicotine.

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

7.6 Questionnaires

The questionnaires will be completed by the subjects (Appendix A). All subject-reported measures as well as instructions will be provided in the subject's local language.

7.6.1 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 as characteristics of the study subjects, to assess their eligibility to participate in the study, and to serve as baseline values.

7.6.2 Fagerström Test for Nicotine Dependence (Revised Version)

Self-reported level of nicotine dependence will be assessed via a questionnaire on Baseline Day -1 using the Fagerström Test for Nicotine Dependence (FTND) in its revised version [24].

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) [24]. This information will be used as characteristics of the study subjects.

7.6.3 ABOUT – Product Experience Questionnaire

Product experience will be assessed via a subject self-reported outcome measure, part of the ABOUT toolbox [25].

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) [26] to RRPs and the Product Evaluation Scale [27].

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).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nausea).
- Enjoyment of respiratory tract sensations (single-item assessment).
- Craving reduction (single-item assessment).

Subjects will be asked to assess the items of the questionnaire on a 7-point scale, ranging from “not at all” to “extremely”. A score for each subscale will be computed based on the scoring rule established by the questionnaire developer [26].

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 is be the face-to-face interview between the subject and study site staff, using open, non-directive questions, as described in section 8.2.

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) is defined as any health-related event which is adverse or unfavorable and which either starts after ICF signature or represents a worsening of a health–related condition that existed at the time of that signature. Careful medical judgment is required to establish whether a clinical finding (including an abnormal laboratory result) is a true AE or just a manifestation of a preexisting health–related condition. An AE may or may not have a causal relationship with the study procedures or with the use of investigational product.

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is an important medical event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate Investigator's medical judgment, they may jeopardize the subject, or the subject may require medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

"Life-threatening" means that the subject was at immediate risk of death from the event. It might have caused death if it had occurred in a more serious form.

8.1.3 Conditions Existent Before the Start of the Period of Collection (ICF Signature)

Concomitant diseases whose severity is increasing after the screening is to be captured as an AE or SAE, depending on if any seriousness criterion is met.

Therapies or surgical interventions including admissions to hospital that had been planned before the ICF signature should not be considered AEs/SAEs.

8.2 Collection and Reporting of Adverse Events

8.2.1 Collection of Information

AEs should be collected mainly via face-to-face interview with the subject by the use of consistent, open, non-directive questions from the investigator(s) or designee(s) (e.g., "How have you been feeling since you were last asked?").

Any non-serious AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the CRF. SAEs that occur during the study must be documented in the subject's medical record, on the AE CRF, and on the SAE form for recording into safety database.

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).

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms.

8.2.2 Period of Collection

AEs (including SAEs) will be collected from the time of ICF signature until the individual EOS for each participant.

Any AEs which 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, as described in section 8.2.6.

8.2.3 Intensity of Adverse Event

The Investigator must assess the intensity of each reported AE according to the following grading scale:

Table 8 Intensity of Adverse Events

Mild:	Easily tolerated, not interfering with normal everyday activities

Moderate:	Interferes with normal everyday activities, but the subject is still able to function
Severe:	Incapacitating and requiring medical intervention

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

The Investigator must assess the causal relationship between the exposure to the IP (P4M3 Gen 2.0 and CIG) and each of the reported AEs, using the classification system and the criteria described below. The same assessment must be made separately to assess the causal relationship between the study procedures and each of the reported AEs:

Not related: The temporal relationship of the adverse event to IP administration or study procedure(s) makes a causal relationship unlikely, or concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Related: The temporal relationship of the adverse event to IP or study procedure(s) makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.5 Expectedness

Any AE assessed as related to the IP (P4M3 or CIG) will be assessed for its expectedness. An AE will be regarded as "unexpected" if its nature or severity is not consistent with information already recorded in section 6.7 of the current Investigator's Brochure [6].

8.2.6 Follow-up of Non-serious and Serious Adverse Events

Any non-serious AE that is ongoing at the time of Discharge or early termination will be followed-up by the Investigator during the Safety Follow-Up Period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). The follow-up of the ongoing non-serious AEs will be done via a phone call performed at the end of the Safety Follow-Up Period. If the subject is not responding at the first phone call additional two additional attempts will be made, then subject will be declared lost to follow-up.

At the end of the 3-day Safety FU Period, all ongoing non-serious AEs will have the outcome documented as "unknown" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner to have his/her ongoing AEs addressed accordingly.

All SAEs will be followed up by the Investigator or designee after the end of the Safety Follow-Up Period, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). In case the subject cannot be reached for additional information related to SAE(s), a total 3 attempts should be performed before the subject will be declared as lost to follow-up.

8.3 Reporting of Serious Adverse Events

Any SAE observed during the period of collection in this study must be reported within 24 hours of first awareness to Sponsor, via email, having the SAE form attached.

Follow-up information should be reported on a new SAE report form, marked as a follow-up report, and submitted to Sponsor according to the same timelines as described above. The follow-up SAE report form must include the minimum information required for form completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported.

The Investigator or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the IEC, according to local regulations.

8.4 Reporting of Other Abnormal Findigs

The other abnormal findings discovered during different clinical assessments (e.g., ECG, spirometry, vital signs, body weight) should be evaluated for the clinical significance by the Investigator/designee based on his/her medical judgement. All abnormal clinically significant test results or clinical examination findings can, at the discretion of the Investigator, be reported as AEs and handled according to the directions from section 8.2.

8.5 Reporting and Follow-Up of Pregnancies

8.5.1 Period of Collection and Follow-up

Pregnancies detected between the time of signature of the ICF and the time before first exposure to the IP will be considered a reason for screen failure. No pregnancy form will be filled in for that case, however the diagnosed pregnancy must be captured in the screen failure page of the CRF.

Any pregnancy detected after enrollment must be reported by the Investigator within 24 hours. This also includes pregnancies spontaneously reported to the Investigator after the end of the study for a subject. A dedicated pregnancy form will be used to report reportable cases of pregnancy.

Any pregnancy that was potentially associated with exposure to IP (P4M3 and CIG) will be followed-up until an outcome is reached (e.g., normal delivery, spontaneous abortion, or voluntary termination), and until 8 weeks after delivery. Any pregnancy complication, adverse pregnancy outcome or maternal complications will be recorded as an AE accordingly.

The procedure outlined in Section 8.3 should be followed to collect pregnancy reports and provide any additional/follow-up information to Sponsor.

8.5.2 Reporting of Pregnancies

The Investigator is responsible for informing the responsible IEC of any pregnancy case that was reported during the study, as determined by local regulations.

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the early termination procedures (section 9.5), as soon as practical after discontinuation and will enter the 3-day Safety Follow-Up Period.

Any AEs or SAEs that are ongoing at the end of the Safety Follow-Up Period will be managed as described in section 8.2.6.

8.7 Investigational Product Malfunction and Misuse

Any occurrence of P4M3 product events, affecting P4M3 Battery Unit, P4M3 Cartridge, or MDEDR, including malfunction or misuse (use not in accordance with its label and instruction) by a subject will be documented by the Investigator. Information regarding P4M3 product events should be actively collected during the study and assessed for severity as Minor or Major:

Minor – Can be resolved easily.

Major – Cannot be resolved.

P4M3 product events will be categorized into: Break, Fluid Leak, Intermittent Loss of Power, Power Problem, Premature Indicator Activation or Other.

Investigational product misuse may result in use-related hazards (section 2.3.3).

Furthermore, any malfunction or misuse of P4M3 that leads to an AE/SAE will follow the same processes as described above.

9 Study Activities

A detailed schedule of assessment can be found in Appendix A. Measurements not conducted at the exact timepoint but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given timepoint.

In general, if no start time for the procedures is provided, then the procedure can be performed at any time during the day.

9.1 Screening Period

9.1.1 Screening Visit (Day -30 to Day -3)

The Screening visit will be performed ≤28 days prior to enrollment at Admission (Day -2). First, the ICF along with study information will be given to the subject. Prior to being asked to sign the consent form, subjects will be given time to review the study information and ask any questions. Once the ICF is signed and dated and timed, the screening procedures can be performed in the order deemed most practical. While it is recommended to complete as many screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed at the Screening visit.

Screening activities and examinations are listed in Table 9.

Table 9 Time Schedule – Screening Visit

Time	Procedures	Additional Information
Start of Procedure	**Screening Visit**	
Prior to any other study procedure	Informed consent process and signature of ICF	
During the Visit	Information on risks of smoking, advice on smoking cessation	
	Inclusion/exclusion criteria	
	Smoking history	Tobacco/Nicotine Product Use History questionnaire
	ECG	
	Spirometry	
	Demographics	
	Medical History/ Concomitant Diseases	

Time	Procedures	Additional Information
Start of Procedure	**Screening Visit**	
	Prior (≤4 weeks) and concomitant medication	
	Physical examination	
	Body height and weight/ BMI	
	Vital signs	
	Serology	HBV, HCV, and HIV
	Collection of blood sample	- Safety panel (hematology, clinical chemistry) - Pregnancy test (all female subjects)
	Collection of spot urine	- Safety panel - Drug test - Cotinine test
	Alcohol breath test	
	Review of eligibility criteria	
	P4M3 demonstration	Without product use
	Identification of current CIG brand	Explain CIG provision for confinement period by subject
	AE/SAE recording	

Abbreviations:
AE = Adverse event; BMI = Body mass index; CIG = Conventional cigarette(s); ECG = Electrocardiogram; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; ICF = Informed consent form; P4M3 = e-cigarette; SAE = Serious adverse event.

If the eligibility criteria are met, the investigational site staff will contact the subject to arrange Visit Day -2 at the site.

9.2 Baseline Period (Enrollment and Randomization)

9.2.1 Admission Day -2

Day -2 should be scheduled within 27 days after Screening visit [2]. The procedures of the Admission visit on Day -2 (Table 10) can be performed in order deemed most practical according to Table 10.

[2] Alternate subjects will have to repeat the Admission Day -2 visit to qualify for randomization. The data of that repeated visit will be captured in the database as "Admission Day -2 visit – Second occurrence".

Enrolment of a subject will take place at Day -2 only if all eligibility criteria are met, after confirmation of a negative pregnancy test (for female subjects only). The confinement period will start after the successful enrolment. All other procedures and data collection will be completed following the enrollment of the subject.

Table 10 Time Schedule – Admission Visit Day -2

Time	Procedures	Additional Information
Start of Procedure	**Admission Visit Day -2**	
Start of the visit	Check-in at site	CIG use will be allowed on site on Day -2
Prior enrolment	Collection of blood sample	- Pregnancy test
	Collection of spot urine	- Drug test - Cotinine test
	Alcohol breath test	
	Body weight	BMI calculation
	Vital signs	
	Smoking history	Tobacco/Nicotine Product Use History questionnaire
	Inclusion/exclusion criteria	
	Information on the risks of smoking, advice on smoking cessation, and briefing on P4M3	
Prior to breakfast	Enrollment	After confirmation of the eligibility of the subject
During the visit	Breakfast	
	Lunch	
	Detailed training on how to use P4M3	Subject can use P4M3 *ad libitum* for approximately 10 minutes per flavor
	Concomitant medication	
	Concomitant disease status	
	AE/SAE recording	
	P4M3 product events	
End of the visit	Subjects remain confined	11:00 PM stop of smoking

Abbreviations:
AE = Adverse event; BMI = Body mass index; CIG = Conventional cigarette(s); P4M3 = e-cigarette; SAE = Serious adverse event.

9.2.2 Baseline Visit Day -1

Baseline exams will be performed, and subjects will be randomized at Baseline Visit. Randomization will take place only for subjects who are willing to comply with study procedures and to use P4M3 or keep abstinent from smoking (SA) for at least 5 days. Table 11 shows the assessments that will be performed at Baseline Visit Day -1.

Table 11 Time Schedule – Baseline Visit Day -1

Time	Procedures	Additional Information
Start of Procedure	**Baseline Visit Day -1**	
Prior to breakfast	Spirometry	
	Collection of blood sample	After ≥6 hours of fasting - Safety panel (hematology, clinical chemistry)
	Collection of spot urine	- Pregnancy test
	ECG	
	Vital signs	
	Concomitant medication	
	Start 24-hour urine collection	For Day -1
	COHb in blood	
	CYP1A2 activity	Intake of caffeine tablet 6 hrs (±15 min) ahead of blood sample collection
Prior to randomization	Breakfast	
During the visit	Randomization	Per IxRS
	FTND	Questionnaire
	Concomitant medication	
	Concomitant disease status	
	AE/SAE recording	
	ABOUT–Product Experience	Questionnaire
	Subjects are informed of their assigned study arm	
	Collection of CIG butts for accountability	
End of visit (11:00 PM)	CIG *ad libitum* consumption stop	Subject remains confined

Abbreviations:
ABOUT = Assessment of behavioral outcomes related to tobacco and nicotine products; AE = Adverse event; CIG = Conventional cigarette(s); COHb = Carboxyhemoglobin; CYP1A2 = Cytochrome P450 1A2; ECG = Electrocardiogram; FTND = Fagerström test for nicotine dependence; IxRS = Interactive web and voice response system; SAE = Serious adverse event.

9.3 Randomized Exposure Period

9.3.1 Exposure in Confinement Period

On Day 1, subjects will be informed about their allocation to a study arm, i.e., either P4M3 CA35, P4M3 CM35, CIG, or SA. Table 12 shows the assessments that will be performed at Day 1, 2, 3, 4, and 5; Table 13 shows the assessments that will be performed at Day 6 ahead of the Discharge from confinement:

Table 12 Time Schedule – Day 1, 2, 3, 4, and 5

Time	Procedures	Additional Information
Start of Procedure	**Day 1, 2, 3, 4, and 5**	
Prior to breakfast	Vital signs	
	COHb in blood	
	Completion of Day -1 urine collection	
	Start of next 24-hour urine collection	Each day of the confinement period. Day 5 collection will be completed in the morning of Day 6, ahead of Discharge
	Day 1 only: Inform subjects on allocated study arm	
During the visit	Breakfast	
	Distribution of the P4M3 Battery Units and Cartridges to subjects in P4M3 arms	
	HPT	P4M3 arms only
	Day 5 only: CYP1A2 activity	Intake of caffeine tablet 6 hrs (± 15 minutes) ahead of the blood sample collection
	Concomitant Medication	
	Concomitant Diseases	
	AE/SAE recording	
	ABOUT–Product Experience	Questionnaire
	P4M3 product events, malfunctions/ misuse	P4M3 arms only
End of visit (11:00 PM)	Collection of CIG butts	Subjects remain confined
	Cartridge/e-liquid use	Subjects remain confined

Abbreviations:

ABOUT = Assessment of behavioral outcomes related to tobacco and nicotine products; AE = Adverse event; COHb = Carboxyhemoglobin; CIG = Conventional cigarette(s); CYP1A2 = Cytochrome P450 1A2; HPT = Human puffing topography; P4M3 = e-cigarette; SAE = Serious adverse event.

At Day 6, following completion of the procedures and examinations (Table 13), the subjects will be discharged for the Safety follow-up period.

Table 13 Time Schedule – Discharge Day 6

Time	Procedures	Additional Information
Start of Procedure	**Day 6**	
Prior to breakfast	Collection of blood sample	After ≥6 hours of fasting - Safety panel (hematology, clinical chemistry) - Pregnancy test (all female subjects)
	Completion of Day 5 urine collection	
	Collection of spot urine	- Safety panel
	Vital signs	
	Spirometry	
	ECG	
During the visit	Breakfast	
	Concomitant medication	
	Concomitant diseases	
	AE/SAE recording	
	Information on the risk of smoking/smoking cessation advice and debriefing on P4M3	
End of the visit	Check-out from site	

Abbreviations:
AE = Adverse event; ECG = Electrocardiogram; P4M3 = e-cigarette; SAE = Serious adverse event.

9.4 Safety Follow-up Period

After Discharge at Day 6, the subjects will enter a 3-day Safety follow-up period during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs will be conducted by the study investigational site as described in section 8.1.2.

9.5 Early Termination Procedures

When a subject is discontinued from the study, all early termination procedures listed in Table 14 are performed unless the subject refuses to perform the assessments or the procedures have already been performed during that study day.

Table 14 Time Schedule – Early Termination Visit

Procedures	Additional Information
Clinical laboratory parameters (hematology, clinical chemistry) blood collection	After ≥6 hours of fasting, if possible - Safety panel - Pregnancy test (female only)
Urine analysis	- Safety panel
Vital signs	
ECG	
Spirometry	
Information on the risks of smoking, advice on smoking cessation and briefing on P4M3	
Concomitant medication	
Concomitant diseases	
AE/SAE recording	
P4M3 product events malfunctions/misuse	P4M3 arms only
Discharge	

Abbreviations:
AE = Adverse event; ECG = Electrocardiogram; P4M3 = e-cigarette; SAE = Serious adverse event

10 Quality Control and Quality Assurance

10.1 Monitoring

The Clinical Research Associate ("Monitor") of the contract research organization (CRO) will be responsible for the monitoring of the study. Monitoring will be performed according to CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

The PI(s) or designee(s) shall permit the Monitor to review study data as frequently as considered necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory met.

The PI(s) or designee(s) shall access medical records for the Monitor in order that entries in the CRFs may be verified. As part of his/her(their) responsibilities, the PI(s) or designee(s) is(are) expected to ensure that the study adheres to GCP requirements [2] .

An Investigator's meeting will be held prior to the site initiation visit. During this meeting, the general training of the study procedures and specific training on selected procedures will be completed and documented.

Subsequently to the Investigator's meeting, and before the first subject is screened into the study, the site initiation visit will be conducted by the Monitor and, if necessary, together with the Sponsor or its authorized representative. The purpose of the site initiation visit is described in the monitoring plan.

During the study, the Monitor will have regular contact with the study site, including interim monitoring visits. The purpose of these visits is described in the monitoring plan.

Communication by telephone, mail, and e-mail may be used as needed to supplement site visits. The Principal Investigator and study personnel will cooperate with the Monitor, provide all appropriate documentation, and will be available to discuss the study.

The Monitor and the Sponsor's personnel will be available between visits should the Principal Investigator or other staff at the sites need information and advice.

Site visits will be made at regular intervals during the study. The frequency of the monitoring visits will be defined in the monitoring plan agreed with the Sponsor.

The PI(s) or designee(s), must be available during the monitoring visit to review the data, resolve any queries and to allow direct access to the subject's records for source data verification.

10.2 Training of Staff

A formal meeting (Investigator's meeting) will be conducted prior to site initiation. During this meeting, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training to the relevant systems and other study-specific procedures. The activities of this meeting will be described in the monitoring plan.

Further to the Investigator meeting, the PI(s) or designee(s) will ensure that appropriate training relevant to the study is provided to all staff involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the staff involved. The PI(s) or designee(s) will maintain a record of all individuals involved in the study.

10.3 Audits and Inspections

Good Clinical Practice regulations require that there are independent inspections of clinical program activities. Such inspections may be performed at any time before, during and/or after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or an IEC may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines [2] , and any applicable regulatory requirements. The PI(s) or designee(s) will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their site.

The PI(s) or designee(s) is(are) responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and/or regulatory agencies. In signing this protocol, the PI(s) or designee(s) understand(s) and agree(s) to provide access to the necessary documentation and files.

10.4 Risk Management

According to ICH-GCP E6(R2) Section 5, the sponsor will implement a system to manage quality throughout all stages of the study process. Pursuant to this, a risk management process will be implemented including identification and scoring of risks, identification of critical data and processes as well as the definition of Key Risk Indicators (KRI) and Quality Tolerance Levels (QTL).

This risk management approach will be described in an Integrated Risk and Quality Management Plan with risks described in a Risk Assessment and Categorization Tool (RACT) which will be developed during the set-up phase of the study and reviewed through all stages of the study.

In addition, at the end of study, the sponsor will describe the quality management approach implemented in the study and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the CSR.

11 Data Management Activities

All data management activities will be described in detail in the data management plan (DMP) and documents specified therein. The electronic systems used to collect subject data and CRF will be FDA 21 CFR Part 11 compliant.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

CRFs are produced by the CRO responsible for Data Management activities (DM-CRO), stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between DM-CRO and the Sponsor (e.g., CD, flash drive, SFTP). This will be documented in the DMP. The subject questionnaires will be completed directly by the subject. Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol in the source documents and DM-CRO will enter the data into the CRF, in accordance with the CRF Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF must be signed by the Investigator to attest that the data contained in the CRF are true and accurate. Any correction made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. The CRF for each subject will be checked against the source documents at the investigational site by the Monitor. Instances of missing or unclear data will be discussed with the Investigator for resolution. A CRF will be generated for all subjects that sign the ICF.

11.1.2 Protocol Deviations

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

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

Information from the source documents will represent the primary source of protocol deviations. Information following investigational site monitoring and other manual reviews will be documented in the investigational site visit reports, follow-up letters, audit documentation, or other manual review and will be recorded and tracked in the CTMS or any other approved format. Telecommunications and other verbal communications regarding deviations will be considered and handled as important communication, documented, and tracked as protocol deviations, as necessary.

Individual entries for protocol deviations that are recorded in the CTMS, or other approved format, following investigational site monitoring and other manual reviews, will be reviewed against the individual data points in the database. The overall procedure for managing protocol deviations is defined in the SOPs and study specific procedures of the DM-CRO. All deviations will be reviewed, as defined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

11.2 Data Handling

All study data will be managed by the DM-CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the DM-CRO. The DM-CRO will prepare the DMP that will be approved by the Sponsor, prior to the start of the study, i.e., First Subject Screened. This document will describe, in detail, the procedures and processes related to data management.

All data of all subjects that are enrolled will be captured and stored in the study database. For screen failures, only the following information should be captured: date/time of ICF signature, date of birth, sex, race, AEs, date, and reason for screen failure.

All data collected during the study is property of the Sponsor, irrespective of the location of the database and the DM-CRO.

The sponsor should ensure that the Investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

The Investigator should have control of all essential documents and records generated by the Investigator/investigational site before, during and after the study.

Additional details are covered in the DMP.

11.2.1 Data Verification

The data will be verified as defined in the DMP and data validation plan (DVP). Data clarification forms (DCFs) will be issued to the investigational site for discrepant or missing data.

All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

Adverse events, concomitant diseases, medical/surgical history, prior/concomitant medication will be classified according to the terminology of the latest version of the following dictionaries, at time of coding the first entry:

Medical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Adverse events / Procedures:	MedDRA®
Medications:	WHO Drug Global

11.2.3 Database Lock

When all outstanding data management issues have been resolved and all validation, quality review and cleaning activities are complete as defined in the DMP, the Sponsor organizes a data review and ensures that the resolution of all raised queries and quality control of the changed data are performed by the CRO before approving the database locked.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the data management and statistical teams at the CRO. Any changes must be documented in the database log file and if these changes may impact the study analysis the PMP process for a database unlock may be requested.

The study database will be transformed into a Clinical Data Interchange Standards Consortium (CDISC) compliant format and transferred to the Sponsor as specified in the DMP and defined in the data transfer agreement. The clinical data will adhere to the CDISC Study Data Tabulation Model (SDTM) Data Structure Specifications.

12 Planned Statistical Methods

12.1 General Considerations

Full details of the statistical analyses will be described in the Statistical Analysis Plan (SAP). Any changes to the planned statistical methods will be documented in the SAP and clinical study report. The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Stratification Criteria

The following stratification factor at baseline will be used in some of the analyses:

- Sex (male and female).

12.1.2 Definitions for Statistical Data Analysis

The following definition will be used for the statistical analysis of safety data:

Term	Definition
Actual exposure arm	Categorical variable representing the actual study arm of enrolled subjects. Non-randomized subjects will be assigned to the category 'Enrolled but not randomized'. Randomized subjects will be assigned to the category corresponding to their randomization study arm. In case of mis-randomization (use of a different product from the allocated one, use of a TNP while being assigned to the smoking cessation arm, or be smoking abstinent while being assigned to the CIG or one of the P4M3 arms), subjects will be assigned to the arm corresponding to their actual exposure.

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by randomization study 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 instead of arithmetic mean, SD, and 95% CI of the arithmetic mean, respectively. Post-baseline

summaries will include change from baseline apart from log-normal variables which will present % change from baseline.

When applicable, the number and % 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 data, the number and % of subjects with missing data, frequency counts, and percentages will be presented.

12.1.4 Handling of Missing Values and of Values outside the Detection Limits

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.

Except otherwise stated, other missing values will not be imputed.
Handling of missing answers to questionnaires will be described in the SAP.

12.2 Product Use

Considering the design of the study, it is expected that, during the exposure period, subjects will only use products corresponding to their randomization arm.

Mis-randomized subjects will be classified according to their actual exposure arm for safety analysis (see section 12.1.2) and excluded from all analyses using the Per Protocol Set.

12.3 Analysis Sets

The following analysis sets will be used for the data analyses.

12.3.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all the 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 after randomization. The FAS will be analyzed by randomized study arm.

12.3.2 Per Protocol Set (PP)

The Per Protocol Set (PP) will be a subset of FAS and include all randomized subjects who fulfill key compliance criteria of the protocol and have no major protocol deviation impacting

the evaluability of the primary objective (to be further described in the SAP). The PP will be analyzed by randomized study arm.

12.3.3 Safety Set (SAF)

The safety population will consist of all the subjects enrolled in the study 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 actual exposure arm (see definition in section 12.1.2).

12.4 Demographics and Baseline Characteristics

Demographics include sex, age, race, body weight, height, body mass index (BMI).

Baseline characteristics include TNP use history, spirometry measurements (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, and FEV_1/FVC), and FTND questionnaire score.

Demographics and baseline characteristics will be summarized as follows:

- By randomization study arm for the FAS,
- By randomization study arm for the PP,
- By actual exposure arm for the SAF.

12.5 Primary Objective

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.

12.5.1 Primary Estimand Analysis

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 without major protocol deviation impacting the evaluability of the primary objective (as defined by the PP).
- Target Population: This is the population of adult smokers who satisfy all eligibility criteria (see section 5.1).
- 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 study 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. Missing data after discontinuation/death will be dealt with as described in section 12.5.1.3.
  - Subjects being tested COVID positive during the study: subjects being tested COVID positive during the study will be included only until the time of the diagnosis or vaccination. Data collected after or at the date of the COVID positive test will be set to missing and dealt with as described in section 12.5.1.3.
  - 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.

12.5.1.1 Baseline Comparability

Demographics and baseline characteristics (as described in section 12.4) will be reported by randomization study arm for the PP.

Given that the study is randomized, demographics and baseline characteristics are expected to be balanced between study arms. Nevertheless, sex and baseline value of the BoExp will be used as covariates in the statistical model (see section 12.5.1.4).

12.5.1.2 Descriptive Analysis

Descriptive statistics as mentioned in section 12.1.3 for the variables of interest and associated changes from baseline will be reported by randomization study arm for the PP and by study day. Descriptive statistics stratified by the factor described in section 12.1.1 will also be computed.

12.5.1.3 Missing Data Strategy

In this analysis, some missing data might occur because of ICEs or because of missing samples, laboratory measurements errors, etc. The main analysis model (see section 12.5.1.4) assumes that subjects with missing data would have outcome data like

those in similar subjects in the same group. This type of assumption is referred to as Missing at Random (MAR). This assumption is aligned with the definition of the primary estimand.

12.5.1.4 Main Analysis

The primary analysis will be conducted in the PP and based on a mixed model for repeated measurements (MMRM). 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 matrix 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), the Day, the randomization study 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 study 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 study 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 2 P4M3 Gen 2.0 CA35 and CM35 study arms combined against the CIG arm and will be used to assess the primary study hypothesis (see section 12.5.1.4.1). Similarly, the exponentiation of the 2 subsequent 'lsmestimate' statements will be used to assess the key secondary objectives 2 and 4 if the procedure of fixed sequence testing allows it (see section 12.6.1).

12.5.1.4.1 Success Criteria

The primary study hypothesis is about demonstrating the reduction of the four BoExp to selected HPHC given in Table 4 in smokers switching from CIG to P4M3 (CA35 and CM35 combined) for 5 days as compared to those who continue smoking CIG. For each individual BoExp, this 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 section 12.5.1.4.

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 BoExp tested in the primary objective given in Table 4.

12.5.1.5 Supplementary Analysis

The model described in section 12.5.1.4 allows contrasting all randomization study arms at Days 1, 2, 3, 4, and 5. While only the contrast between the two P4M3 arms combined and CIG at Day 5 will be used for the primary objective assessment, the following pairwise comparisons at Days 1, 2, 3, 4, and 5 will also 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

Note that 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 12.5.1.4. These contrasts will be used to assess the key secondary objectives 2 and 4 if the procedure of fixed sequence testing allows it (see section 12.6.1).

12.5.2 Secondary Estimand Analysis

This analysis refers to the secondary estimand of the primary objective defined in section 3.1. This estimand is implementing 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 PP. 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 (see section 5.1).

- 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.

12.5.2.1 Baseline Comparability

Demographics and baseline characteristics (as described in section 12.4) will be reported by randomization study arm for the FAS.

Given that the study is randomized, demographics and baseline characteristics are expected to be balanced between study arms. Nevertheless, sex and baseline value of the BoExp will be used as covariates in the statistical model (see section 12.5.2.4).

12.5.2.2 Descriptive Analysis

Descriptive statistics as mentioned in section 12.1.3 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 12.1.1 will also be computed.

12.5.2.3 Missing Data Strategy

In this analysis, some missing data might occur because of missing samples, laboratory measurements errors, etc. The main analysis model (see section 12.5.2.4) assumes that subjects with missing data would have outcome data like those in similar subjects in the same group (MAR assumption). This assumption is aligned with the definition of the secondary estimand.

12.5.2.4 Main Analysis

This analysis will be conducted using the same model as the one described in section 12.5.1.4, except that it will use the FAS instead of the PP and all available data will be included in the model.

In section 12.5.1.4.1, 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.

12.5.2.5 Supplementary Analysis

The model described in section 12.5.2.4 allows contrasting all randomization study arms at Days 1, 2, 3, 4, and 5. All the following 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

Like what will be done for 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 12.5.1.4. These contrasts will be used exploratorily to assess the key secondary objectives 2 and 4 if the procedure of fixed sequence testing allows it for the FAS (see section 12.6.1).

12.6 Secondary Objectives

12.6.1 Key Secondary Objectives

The 1st key secondary objective of the study is to demonstrate the reduction of additional BoExps to selected HPHC given in Table 5 in smokers who switch from CIGs to P4M3 use compared to those who continue to smoke CIG. The statistical analysis for each of these additional BoExp will done similarly to those belonging to the primary objective (except the Success Criteria described in section 12.5.1.4.1). More specifically, the analyses described as primary estimand (see section 12.5.1) and secondary estimand (see section 12.5.2) can be repeated, replacing the endpoints listed in Table 4 by those of Table 5.

The analysis of the 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 (see Figure 3). This first key secondary objective will only be tested if the primary objective is demonstrated. This fixed sequence of study hypotheses ensures that the overall study-wise risk of type I error is preserved at the 2.5% (see section 12.9.3). 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 listed in Table 5.

If both the primary and first key secondary objectives are declared successful, then the 2nd key secondary objective will be tested with type I error level of 2.5%, this time using the contrast CA35 vs. CIG (also obtained from the model described in section 12.5.1.4) and the BoExp listed in Table 4. If this 2nd key secondary objective is also declared successful, then the 3rd key secondary objective can be tested similarly, this time with the BoExp listed in Table 5. The analysis will proceed similarly for the 4th and 5th key secondary objectives (except that the contrast will be CM35 vs. CIG), provided that all preceding objectives are declared successful (fixed sequence testing). If, along the procedure from the primary objective up to the last key secondary objective, any of the objectives are not declared successful, the sequence testing will stop, and further testing will not be permitted.

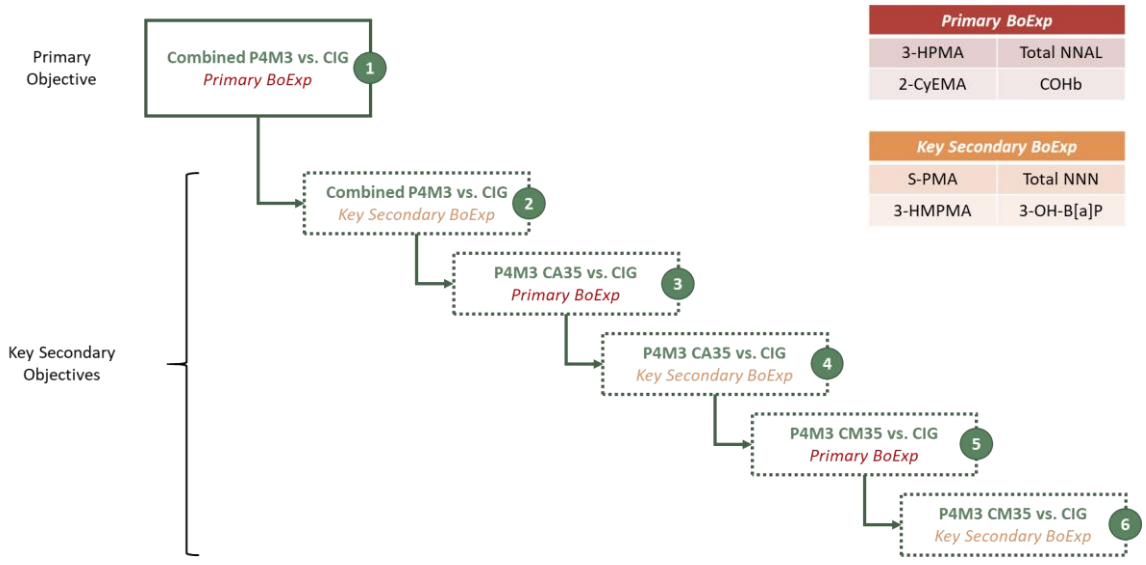


Figure 3 Representation of the Procedure of Fixed Sequence Testing

Note that, at each level of testing, all BoExp need to lead to a statistically significant test. If the statistical test for one of the BoExp does not reach statistical significance (at the 2.5%

level), then the corresponding level of testing cannot be declared successful, and the fixed sequence testing will stop.

The formal testing procedure of this study will use the primary estimand based on the PP (see section 12.5.1). The procedure will be repeated exploratorily using the secondary estimand based on the FAS (see section 12.5.2).

12.6.2 Secondary Objective

This analysis refers to the secondary objective defined in section 3.2.2 about safety. All safety analyses will be conducted on the SAF (inferential analyses will not be performed on safety endpoints).

All safety data will be provided in listings by actual exposure arm, 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
- Follow-up: from Day 6 (Discharge) to end of Safety follow-up

Unless otherwise specified, summaries will be produced by actual exposure arm and safety periods.

Adverse event data will serve as 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, body weight, and BMI.

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 safety population overall and by safety period. Summaries will also be presented for AEs leading to product discontinuation, AEs leading to study discontinuation, AEs by relatedness to product exposure (including expectedness) and relatedness to study procedures, AEs by severity, and AE by action taken related to the product. Tabulations will be performed for both the number of subjects experiencing an event and the number of events for the SAF.

With respect to device malfunctions, the number and % of subjects with device events will be tabulated. The number and % of subjects with device events overall, leading to an AE, a SAE, discontinuation, or to non-adherence will also be tabulated.

Descriptive statistics as defined in section 12.1.3 for actual values and changes from baseline will be produced for the following parameters: vital signs, ECGs, spirometry, clinical chemistry, hematology, urinalysis safety panel, body weight, and BMI.

12.7 Exploratory Objectives

The exploratory objectives defined in sections 3.3.1, 3.3.2, and 3.3.6 will be analyzed similarly to the primary objective (except that there will be no success criteria). More specifically, for all endpoints expressed on the continuous scale, the analyses described as primary estimand (see section 12.5.1) and secondary estimand (see section 12.5.2) will be repeated.

Except for CYP1A2 enzymatic activity, 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.

For the exploratory objective (section 3.3.6), the CYP1A2 enzymatic activity will only be measured at baseline and at Day 5. Thus, the REPEATED statement described in sections 12.5.1.4 and 12.5.2.4 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.

For the exploratory objectives defined in section 3.3.3, 3.3.4, and 3.3.5, only descriptive statistics will be computed for both the PP and FAS.

12.8 Interim Analysis

In this study, no interim analysis is planned.

12.9 Measures to Control Bias

12.9.1 Method for Assigning Subjects to Study Arms

Randomization will be used to assign subjects to study arms. Given that the study is randomized, demographics and baseline characteristics are expected to be balanced between study arms. Nevertheless, sex and baseline value of the BoExp will be used as covariates in the statistical models (see sections 12.5.1.4 and 12.5.2.4).

12.9.2 Blinding

This is an open-label study. Therefore, the subjects and Investigators or designees or staff 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. PMI and contract research organization (CRO) personnel will be blinded to the self-selected groups as summarized in Table 15.

Table 15 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.
PMI clinical scientist	Blinded to all BoExp data	After the SAP 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.

Any PMI and CRO personnel who are not listed in the above table will not be blinded to the study data.

Unblinded information will not be shared with the blinded study team, until the end of the blinding period. PMI will receive blinded and unblinded data for the pre-analysis data review as planned in the data review plan. Blinded data will be accessible by the blinded study personnel in a masked format or presented independently of the subject identifier to ensure that data cannot be associated to a subject. Unblinded data will only be reviewed by the unblinded study team.

12.9.3 Study Significance Level and Multiple Testing Procedures

In this study, the overall familywise 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 at the 2.5% type I error level until one of the objectives is rejected and no further testing will be performed (in this case, only subsequent exploratory testing will be conducted).

The primary study hypothesis (as assessed using the primary estimand defined in section 12.5.1) will be tested one-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 4 that are part of the primary study hypothesis (all need to pass for the objective to be considered as demonstrated).

If the primary study hypothesis is demonstrated, 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 provided. This will be applied to all BoExps of Table 5 that are part of the 1st key secondary study hypothesis (all need to pass for the 1st key secondary objective to be successful).

If the primary study hypothesis is not demonstrated, the 1st key secondary hypothesis (and all subsequent key secondary objectives) will be considered exploratory and conducted 2-sided at the α-level of 5% and the associated 2-sided 95% confidence interval will be provided.

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

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

12.9.4 Determination of Sample Size and Power Consideration

In this study, 72 subjects will be 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 cigarette developed by PMI which is likely to be less risky than cigarette; ClinicalTrials.gov identifiers are NCT01970995, NCT01989156, NCT01959932, and NCT01970982, respectively), Table 16 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 than 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 16, 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 16. 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 16. These provide indications on the expected precision on the estimates of the ratios.

Table 16 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 (JP)	2CyEMA	18.23	32.43	>99%	>99%	4.9	25.4
	3-HPMA	50.67	32.72	>99%		13.8	71.0
	COHb	44.94	17.24	>99%		6.0	53.8
	Total NNAL	43.69	26.09	>99%		9.2	57.1
1989156 (US)	2CyEMA	17.23	42.01	>99%	>99%	6.2	26.3
	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 (EU)	2CyEMA	13.16	34.41	>99%	>99%	3.8	18.7
	3-HPMA	41.63	26.1	>99%		8.7	54.4
	COHb	23.45	16.84	>99%		3.1	28.0
	Total NNAL	43.54	27.13	>99%		9.6	57.5
1970982 (JP)	2CyEMA	21.21	43.16	>99%	>99%	7.9	32.7
	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%		18.0	75.3

Table 16 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 17 displays the power estimates for the 1st key secondary hypothesiswith a power of at least 99%.

Table 17 Power Computations 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 (JP)	3-HMPMA	43.06	35.59	>99%	>98%	12.9	62.0
	3-OH-B[a]P	27.19	43.93	>99%		10.4	42.0
	S-PMA	10.97	46.63	>99%		4.5	17.4
	Total NNN	27.02	61.84	>99%		15.5	49.1
1989156 (US)	3-HMPMA	38.26	53.56	>99%	>98%	18.4	64.6
	3-OH-B[a]P	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 (EU)	3-HMPMA	22.54	30.76	>99%	>98%	5.7	30.9
	3-OH-B[a]P	27.5	46.17	>99%		11.1	43.5
	S-PMA	5.99	37.3	>99%		1.9	8.8

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 (%)
1970982 (JP)	Total NNN	24.12	95.15	>99%	>98%	22.9	55.7
	3-HMPMA	37.71	49.07	>99%		16.4	61.6
	3-OH-B[a]P	29.99	52.2	>99%		14.0	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 18 and Table 19). As per Table 18 and Table 19 the power was of 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 18 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 (JP)	2CyEMA	18.23	32.43	>99%	>95%	6.1	26.9
	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 (US)	2CyEMA	17.23	42.01	>99%	>95%	7.8	28.3
	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	71.0
1959932 (EU)	2CyEMA	13.16	34.41	>99%	>95%	4.7	19.8
	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 (JP)	2CyEMA	21.21	43.16	>99%	>95%	9.9	35.0
	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 19 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 (JP)	3-HMPMA	43.06	35.59	>99%	>94%	16.0	65.9
	3-OH-B[a]P	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 (US)	3-HMPMA	38.26	53.56	>99%	>94%	23.2	70.4
	3-OH-B[a]P	28.94	54.77	>99%		18.2	54.2
	S-PMA	12.58	69.68	>99%		10.7	27.3

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 (%)
1959932 (EU)	Total NNN	14.06	78.93	>99%	>94%	14.0	33.1
	3-HMPMA	22.54	30.76	>99%		7.1	32.6
	3-OH-B[a]P	27.5	46.17	>99%		14.0	47.2
	S-PMA	5.99	37.3	>99%		2.4	9.3
1970982 (JP)	Total NNN	24.12	95.15	>99%	>94%	30.0	64.6
	3-HMPMA	37.71	49.07	>99%		20.6	66.5
	3-OH-B[a]P	29.99	52.2	>99%		17.8	55.1
	S-PMA	15.68	49.76	>99%		8.8	27.9
	Total NNN	30.06	67.69	>99%		24.6	63.8

13 Administrative Considerations

13.1 Study Administrative Structure

13.1.1 Sponsor

The list of sponsor personnel will be provided as a separate document.

13.1.2 List of Principal Investigators and Sites

The list of principal investigators and sites will be provided as a separate document.

13.2 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the subject. An agreement to disclose any such information will be obtained from the subject in writing and signed by the subject, in compliance with all local and national data protection and privacy legislation.

The anonymity of subjects participating in this study will be maintained. Subjects will be identifiable by the Sponsor (or Sponsor's authorized representative) on CRFs and other documents by their subject (or randomization) number/code, sex, and date of birth, but not by name, initial, or any other details relating to identifiable person (e.g., address, social security number, medical chart number, etc.). The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

Any documents that allow full identification of the subject (e.g., the subject's signed ICF) must be maintained in confidence by the Principal Investigator or designee. If any document relating to this study shows a subject's name or any other details relating to an identifiable person (e.g., address, social security number, medical chart number, etc.), the name or other identifiable details must be obscured before a copy of that document is supplied to the Sponsor or the Sponsor's authorized representative.

13.3 Access to Source Documents

Subjects will be informed that, during as well as after the course of the clinical study, the Sponsor, any authorized representatives of the Sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected and ensure that all personal information made available for inspection is handled in the strictest confidence and in accordance with national and local data protection and privacy legislation.

The PI(s) and all study site staff involved with the study must permit direct access to source data/documents for study related monitoring, audits, IEC review, and regulatory inspection(s).

13.4 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans, and ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study, and the actions taken will be maintained by the Investigator/study site for the study, as required by ICH GCP [2] and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in Section 8 of the ICH Tripartite Guideline for Good Clinical Practice [2] .

Essential documents must be retained by the Investigator for a minimum of:

- At least 15 years after completion or discontinuation of the study.

These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

Examples of essential records/documents include, but are not limited to:

- Signed informed consent documents for all subjects and master ICF.
- Subject identification code list, screening log, and enrollment log (if applicable).
- Record of all communications between the Investigator and the IEC, composition of the IEC.
- Record of all communications/contact between the PI(s) or designee(s), Sponsor, and its authorized representatives.
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curricula vitae, and their signatures.
- Investigator logs.
- CRFs, study specific questionnaires (and associated data/scoring), subject diaries.
- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents (e.g., ECGs, consultation reports, physical examination, laboratory records) or any electronically captured study source data.
- Clinical laboratory reports, laboratory normal ranges.
- Original medical/hospital records, if applicable (the medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or study site).

- Device issue log, IP accountability logs, dispensing records.
- Information regarding subjects' discontinuation and any follow-up.

It is the responsibility of the Sponsor to inform the PI(s)/study site(s) as to when these documents no longer need to be retained.

The PI(s)/study site(s) must take measures to prevent accidental or premature destruction of these documents.

If the PI(s) wish(es) to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

The PI(s) or designee(s) must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the archives of the PI(s). If a Principal Investigator is unable to meet this obligation, he/she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

The Sponsor or Sponsor's authorized representative will maintain documentation relating to the study for as long as the IP is on the market, and/or for 15 years after the CSR has been finalized.

13.5 Clinical Study Report

The Sponsor must ensure that a CSR for this study is prepared regardless of whether the study is completed or prematurely terminated.

The CSR will be written based on standards of the ICH Guideline for the structure and content of clinical study reports. In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IEC will be complied with as requested by local requirements.

The results of the additional variables for analysis will be presented in reports separate from the study CSR.

13.6 Financial Disclosure

Principal Investigator(s) and any designees are required to provide financial disclosure information to the Sponsor. In addition, the Investigators and designees must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the study and for one year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains information that is confidential and proprietary to the Sponsor. This information is being provided solely for the purpose of evaluation and/or conducting this study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IEC, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice must be given to the Sponsor prior to any such disclosure.

The study will be registered and published in a WHO primary register or at www.clinicaltrials.gov.

13.8 Insurance

The Sponsor is responsible for AEs and health damage to patients associated with the investigational products that are used during the study, except for AEs and health damage to patients caused by a negligent or an intentional misconduct and/or significant deviation to the protocol of the Investigator or the clinical study site or the patients. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

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Appendices

Appendix A 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)	•		•						•	•	

	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**
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) 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

PHILIP MORRIS PRODUCTS S.A.

Appendix B Participating Laboratories

Safety Laboratory

[redacted]

Bioanalytical Laboratory

[redacted]

Appendix C Human Puffing Topography Parameters

Per-Puff Parameters

Description	Variable	Unit
Puff ID	Ni	
Puff volume	Vi	mL
Puff duration	Di	s
Average puff flow	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

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	∑ Qci / NPC, i=1 … NPC	s
Total puffing duration (total product use duration, session length)	TDFi	∑ DFi	s
Puff Frequency	PFeq	NPC/(TDFi/60)	
% of puffs with higher power setting	PctPuffsHighPow	100*Count Ni at high power/NPC	%

Appendix D Clinical Laboratory Parameters Safety Panel

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

* Except at Screening where non-fasting glucose can be assessed

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