PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

P4M3-PK-02-US

Study Title:	A single-center, open-label, concentration-ranging study to investigate the nicotine pharmacokinetic profiles and pharmacodynamic effects of the P4M3 variants in relation to subjects' own electronic cigarettes in healthy, adult experienced users of electronic cigarettes
Short Name:	Concentration-ranging study to investigate the nicotine pharmacokinetic profiles and pharmacodynamic effects of P4M3 variants
Study Number:	P4M3-PK-02-US
Registration number:	Not assigned
Product name:	P4M3
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number / Date:	2.0, Final Protocol, Amendment 1 / 10 Jul 2017 1.0, Final Protocol / 15 Jun 2017
Author:	[redacted], Ph.D. Senior Scientist, Protocol and Medical Writer, [redacted].

PROTOCOL REVISION HISTORY

Date/Name	Description
10 Jul 2017 Thelma Ward	**Final Protocol, Amendment 1 (Version 2.0)** The protocol has been amended to reflect changes with regards to verbiage concerning ventilation requirements for the study as the assigned clinical site has an adequate ventilation system for the purposes of this study. Additionally, text within the protocol has been updated with regards to subject discontinuation and to the subject information sheet being an integral part of the informed consent form. Section 1.1 - Institutional Review Board (IRB) Approval The first sentence in this section has been updated as follows (deleted text in strikethrough font): "Prior to the start of the study, the clinical study protocol, together with its associated documents (ICF, ~~subject information,~~ subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Investigator's curriculum vitae [CV] and/or other evidence of qualifications and any other documents requested by an Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IRB." Section 1.3.1 - Study Consent The third paragraph has been updated as follows (deleted text in strikethrough font): "If a protocol amendment is required, or if new information regarding the risk profile of the IP becomes available, an amendment to the ICF ~~and subject information~~ may be required. If revision of the ICF ~~and subject information~~ is necessary, the Investigator will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IRB before subjects are required to re-sign the ICF." Section 6.3.5 - Stopping Rules for Investigational Product The section has been updated as follows (deleted text in strikethrough font, updated text added in bold font): "For safety purposes, use of the IPs should be temporarily reduced or stopped in the event of any signs suggesting nicotine overexposure, e.g., gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach, or abdominal pain), cold sweats, headache, dizziness, and breathing problems or any reasons at the discretion of the Investigator. ~~If the IP is reduced or stopped, the reasons for discontinuation should be documented in the source documents and subjects will undertake early termination~~

	~~procedures.~~ **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)." Section 6.7.1 - Nicotine/Tobacco Product Restrictions This section has been updated as follows (deleted text in strikethrough font): "Subjects will not be allowed to use any nicotine/tobacco-containing products except their own closed tank/cartridge e-cigarette on Day -1 and the P4M3 test products as required per protocol from Days 1 to 4 through Discharge on Day 5 or early termination. ~~On Day -2 and on Days -1 to 4, to avoid nicotine cross contamination, every subject must use the assigned product alone with an interval between subjects allowing ventilation of the room.~~" Section 7.1 - Informed Consent The section has been updated as follows (deleted text in strikethrough font, updated text added in bold font): "Each subject must give his/her informed consent prior to participating in the study (i.e., at the Screening Visit). During the consent process, the Investigator or designee obtaining consent must inform each subject of the nature, risks, and benefits of, and alternatives to study participation. In addition, each subject must review the ~~Subject Information Sheet and~~ **subject information provided within the** ICF and must have sufficient time to read and understand and have adequate opportunity to ask questions. The ICF must be signed, dated, and timed prior to undertaking any study-specific procedures. A signed copy must be given to the subject."
15 Jun 2017 Thelma Ward	**Final Protocol (Version 1.0)**

SYNOPSIS

Sponsor:

Philip Morris Products S.A.

Name of Product:

P4M3

Study Title:

A single-center, open-label, concentration-ranging study to investigate the nicotine pharmacokinetic profiles and pharmacodynamic effects of the P4M3 variants in relation to subjects' own electronic cigarettes in healthy, adult experienced users of electronic cigarettes

Short Study Title:

Concentration-ranging study to investigate the nicotine pharmacokinetic profiles and pharmacodynamic effects of P4M3 variants

Study Number and Acronym:

P4M3-PK-02-US, no acronym

Objectives and Endpoints:

Primary Objective and Endpoints

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

Endpoints:

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

Secondary Objectives and Endpoints

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

Endpoints:

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

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

Endpoints:

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

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

Endpoint:

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

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

Endpoints:

- Theoretical nicotine exposure calculated as total puff volume [mL] (from HPT) x nicotine [µg/mL] (deriving the nicotine [µg/mL] from the CORESTA [Cooperation Centre for Scientific Research Relative to Tobacco] regimen to determine the nicotine [µg] per puff [55 mL]) for each of the P4M3 variants.
- cC_{peak} - cC_{trough} versus theoretical rate of nicotine inhalation (R_0) (60 minutes *ad libitum* use only)
- $cAUCb_{(0-4h)}$ versus theoretical nicotine exposure (60 minutes *ad libitum* use only)
- cC_{max} versus theoretical rate of nicotine inhalation (R_0) (fixed puffing regimen only)
- $cAUC_{(0-4h)}$ versus theoretical nicotine exposure (fixed puffing regimen only)

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

Endpoints:

- HPT parameters: total puff volume, average flow, average puff duration, average puff volume

- $cC_{average}$ (60 minutes *ad libitum* use only)
- $cAUCb_{(0-4h)}$ versus HPT parameters (60 minutes *ad libitum* use only)
- cC_{peak} - cC_{trough} versus HPT parameters (60 minutes *ad libitum* use only)
- cC_{max} versus HPT parameters (fixed puffing regimen only)
- $cAUC_{(0-4h)}$ versus HPT parameters (fixed puffing regimen only)

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

Endpoint:

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

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

Endpoints:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Frequency of AEs and SAEs
- Incidence of P4M3 device events including malfunction/misuse
- Physical examination changes from baseline
- Changes from baseline of VAS, three Likert scales and the open question of Cough assessment questionnaire
- Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, QTcB , QTcF intervals)
- Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Spirometry changes from baseline (forced expiratory volume in 1 second [FEV_1], FEV_1 % predicted, forced vital capacity [FVC], FEV_1/FVC)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel (described in Table 2)
- Concomitant medications

Study Hypothesis:

There are no statistical hypotheses to be tested.

Study Design:

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

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

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

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

- a fixed puffing regimen comprising of 12 puffs in total at a rate of one puff every 30 seconds (± 5 seconds) with HPT recording in the morning.
- *ad libitum* use for 60 minutes (± 5 minutes) with HPT recording in the afternoon

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

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

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

Sequence 1:
P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA
Sequence 2:
P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA

On Days 1 to 4, subjects will be provided and instructed to use a new, ready-to-use product (full cartridge) of the assigned P4M3 variant for fixed puffing regimen with HPT recording in the morning and another new one for the *ad libitum* use for 60 minutes with HPT recording in the afternoon, according to one of two randomly assigned sequences. The concentration of P4M3 e-liquid will be the same on a given day for fixed puffing and *ad libitum* use on Days 1 to 4. During confinement, the

use of nicotine/tobacco containing products other than the one allocated during the scheduled use periods will not be allowed.

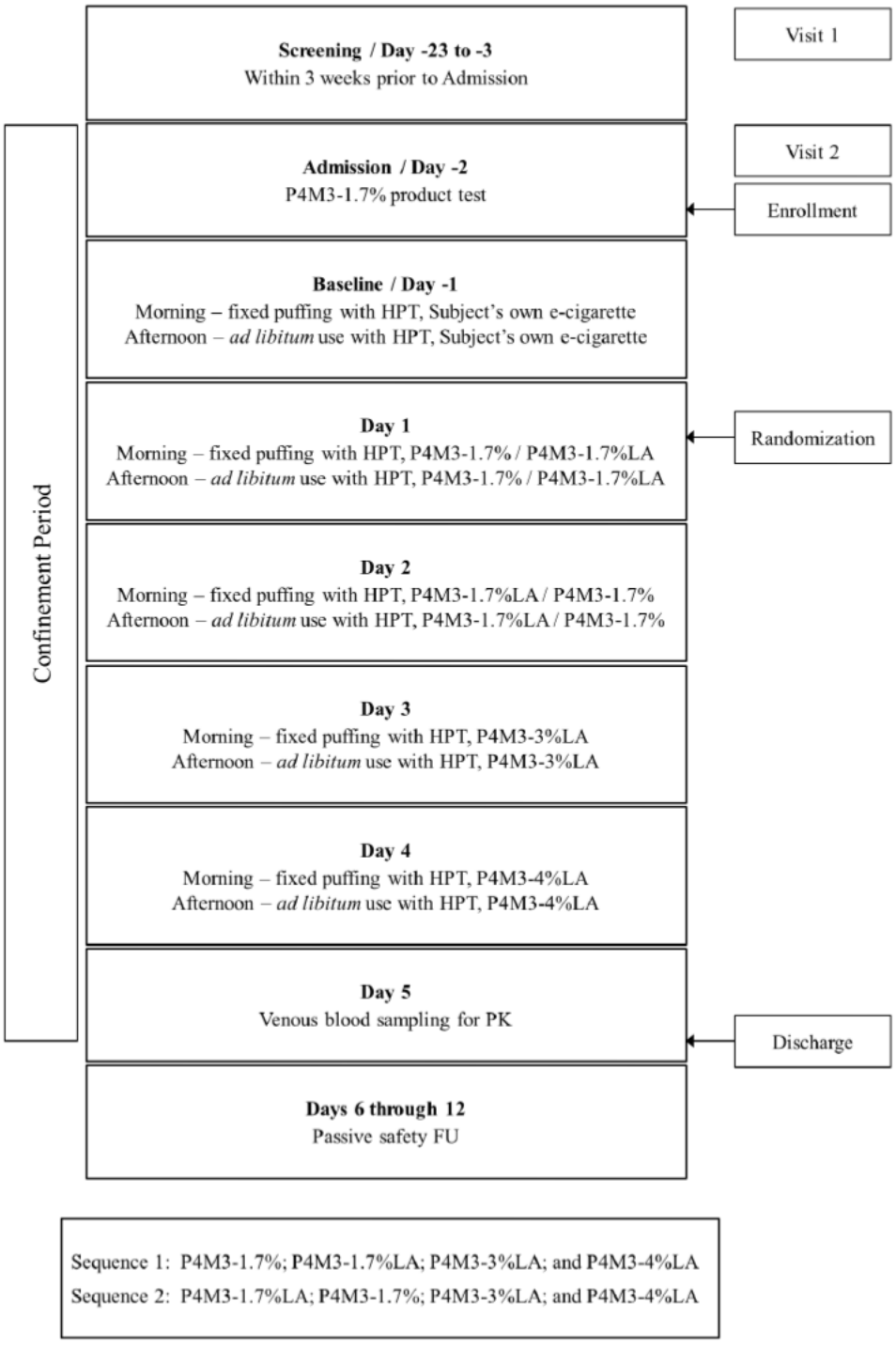
Venous blood samples will be taken for analysis of PK parameters prior to the start of and during both fixed puffing and the 60 minutes *ad libitum* use at specified time points before and after T0 on Day -1 to Day 4. Blood sampling for the determination of nicotine and derived PK parameters will be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

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

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

The study schematic is presented in Figure 1. The schedule of events is provided in Appendix 1.

Figure 1 Study Schematic



Study Population and Criteria for Inclusion:

Healthy adult users of e-cigarettes meeting the following main inclusion criteria:

1. Subject has signed the informed consent form (ICF) and is able to understand the information provided in the ICF.
2. Subject is 21 to 65 years of age, inclusive, at the Screening Visit.
3. Subject is White.
4. Subject is a former daily cigarette smoker who smoked at least 100 cigarettes or more in his/her life and ceased smoking at least 3 months prior to the Screening Visit.
5. Subject has been using a commercially available, nicotine-containing closed tank/cartridge e-cigarette daily for at least 3 months prior to the Screening Visit.
6. Subject has a urine cotinine test ≥200 ng/mL at the Screening Visit and Admission.
7. Subject does not plan to quit using e-cigarettes during the study.
8. Subject is ready to comply with study procedures.
9. Subject is ready to accept periods of interruption of nicotine use.
10. Subject is ready to accept using the P4M3 product variants as instructed and for the duration of the study.

Criteria for Exclusion:

1. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition (including safety laboratory as per Common Terminology Criteria for Adverse Events [CTCAE]), which as per the judgment of the Investigator would jeopardize the safety of the subject).
2. Subject has abnormal renal function test result or subject with a creatinine clearance <60 mL/minute (as determined by the Cockcroft-Gault) at the Screening Visit, confirmed on repeat testing.
3. Subject has elevated liver function test results (alanine transaminase [ALT] or aspartate transaminase [AST] >2X upper limit of the normal range [ULN]) at the Screening Visit;
4. Subject has bilirubin >1.5X ULN (isolated bilirubin >1.5X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at the Screening Visit.
5. Subject has FEV_1/FVC <0.7 and FEV_1 <80% predicted value at post-bronchodilator spirometry at the Screening Visit.
6. Subject has asthma condition (FEV_1/FVC <0.75 and reversibility in FEV_1 >12% and > 200 mL from pre- to post-bronchodilator values) at the Screening Visit.
7. Subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug (whichever is longer) prior to Admission which has an impact on cytochrome P450 (CYP) 2A6 activity.
8. Subject has a carbon monoxide (CO) breath test ≥ 10 ppm at the Screening Visit or Admission.

9. Subject has a positive alcohol test at the Screening Visit or Admission and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in study.
10. Subject has a positive urine drug screen at the Screening Visit or Admission.
11. Subject has a body mass index (BMI) <18.5 kg/m^2 or BMI ≥35 kg/m^2 at the Screening Visit.
12. Subject has a positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B, or hepatitis C at the Screening Visit.
13. The subject has a baseline QTcF >450 ms for males or >470 ms for females at the Screening Visit or history of congenital long QT syndrome, or Torsades de Pointes.
14. Subject has abnormal (clinically significant) ECG findings at the Screening Visit. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by the Investigator.
15. Subject or one of their family members* is a current or former employee of the tobacco industry.
16. Subject or one of their family members* is an employee of the investigational site or any other parties involved in the study.
17. Subject has participated in a clinical study within 3 months prior to the Screening Visit.
18. Subject has been previously screened in this study and failed to meet the eligibility criteria.
19. Subject smokes combustible cigarettes or other tobacco products (with the exception of commercially available, nicotine containing closed tank/cartridge e-cigarettes).
20. Subject is using estrogen-containing medication.
21. Female subject of childbearing potential who is pregnant or breastfeeding.
22. Female subject of childbearing potential who does not agree to use an acceptable method of effective contraception**. Female subject who is not of childbearing potential must meet at least one of the following criteria:
    - has undergone hysterectomy or bilateral tubal ligation,
    - has medically confirmed ovarian failure, or
    - is medically confirmed to be postmenopausal (cessation of regular menses for at least 12 consecutive months prior to Admission with no alternative pathological or physiological cause).

*As defined by the US Food and Drug Administration (FDA) guidance 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"

**Acceptable methods of effective contraception:
Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from the Screening Visit until the end of the passive safety FU. Hormonal contraception

with estrogen containing products is NOT allowed in this study.

A sufficient number of eligible subjects will be enrolled to randomize 16 subjects to use P4M3 variants according to one of two sequences. The randomization scheme will be generated at Celerion by a statistician using a computerized program. At least 5 subjects of each sex will be randomized.

Subjects discontinued after randomization will not be replaced.

Investigational Products:

Test products:

P4M3 with e-liquid concentrations of:

1.7% nicotine without lactic acid	(P4M3-1.7%)
1.7% nicotine with 1.1% lactic acid	(P4M3-1.7%LA)
3% nicotine with 1.1% lactic acid,	(P4M3-3%LA)
4% nicotine with 2% lactic acid	(P4M3-4%LA)

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

Reference product:

Subject's own e-cigarette with e-liquid:
Commercially available, closed tank/cartridge e-cigarette.
Subject will be asked to buy the anticipated amount of e-cigarette (e-liquid) for the study.

Duration of Study:

The entire study per subject will last between 15 to 36 days, including a Screening Visit of up to 3 weeks (Day -23 to Day -3) prior to Admission, 1 day of Admission (Day -2), 5 days of product use (Days -1 to 4), and 7 days of passive safety FU.

Statistical Methods:

All endpoints will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data, arithmetic means and standard deviations (mean and SD), median, minimum and maximum, for log normally distributed endpoints geometric mean, geometric coefficient of variation (CV) will also be presented (note: categorical variables will be summarized by frequency statistics [number and percentage]). All analyses and summaries will be performed separately for fixed puffing regimen and *ad libitum* use, with the exception of AEs. In addition, PK, PD, and safety variables will be analyzed as follows:

Pharmacokinetic Analysis:

Nicotine plasma PK parameters will be determined from the plasma concentration-time profiles for all evaluable subjects according to conventional Non-Compartmental Analysis (NCA) methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. For both, the fixed puffing regimen and the *ad libitum* use, background-corrected nicotine plasma concentrations will be used for the estimation of plasma PK parameters by NCA.

Plasma PK parameters will be summarized using descriptive statistics by study product (e.g., subject's own product or P4M3 variant), as appropriate.

For the 60-minute *ad libitum* uses, an analysis of variance (ANOVA) will be conducted on logarithmically transformed cC_{peak}, $cC_{average}$, and $cAUCb_{(0-4h)}$, as applicable. The model will be adjusted for sex and cC_{trough} value with product use as a fixed effect and subjects as a random effect. Wilcoxon signed-rank test will be used to compare t_{peak} between the test (P4M3 variant) and reference (subject's own) products.

For the fixed puffing regimens, the ratio of geometric mean nicotine exposure normalized $cAUC_{(0-4h)}$ and cC_{max} for each P4M3 variant in reference to the subject's own e-cigarette will be presented with associated 90% confidence intervals (CIs). The theoretical nicotine exposure, as appropriate, will be used for the purposes of parameter normalization.

In order to evaluate the PK parameters of the P4M3 variants with subjects' own e-cigarette, an ANOVA will be conducted on logarithmically transformed $cAUC_{(0-4h)}$, $cC_{average}$, and cC_{max}, as applicable. The model will include sex and product use as fixed effects and subjects as a random effect. For each P4M3 variant, the geometric least-squares means (LSM) P4M3 variant:e-cigarette ratios will be presented with 90% CIs. The dose-proportionality of the e-liquid concentrations (with lactic acid only) versus nicotine exposure PK parameters will be investigated graphically on an exploratory basis.

In addition, the impact of the lactic acid will be evaluated for the PK parameters, using an ANOVA on logarithmically transformed $cAUC_{(0-4h)}$ and cC_{max}, adjusting for sex, with sequence, subject nested within sequence, period, and product as fixed effects. The geometric LSM P4M3-1.7%LA:P4M3-1.7% ratios will be presented with 90% CIs. Wilcoxon signed-rank test will be used to compare t_{max} between the study products.

Pharmacodynamic Analysis:
PD will be summarized by study product.

- VAS craving assessments will be summarized over time within each of the fixed puffing regimen and *ad libitum* use. The scores will be assessed using an Analysis of Covariance (ANCOVA) model with product use, sex, baseline value prior to product use, and the interaction of product and time point as fixed effects and subjects as random effect including the assessment time points as repeated measurements. The interaction term will be removed if $p > 0.1$. The summary statistics will include least square means as well as arithmetic means. Additionally, the VAS craving score will be analyzed as AUC (similar to the calculation of $AUC_{(0-4h)}$, averaged over the total time of VAS collection period) and analyzed using the same model approach as for the PK parameters.
- Adapted mCEQ subscale scores and SQ answers will be summarized with descriptive statistics and displayed graphically by product. The scores/answers will be analyzed using an ANOVA adjusted for sex with product use as a fixed effect and subjects as a random effect. HPT parameters will be summarized by product use period with geometric means, % coefficient of variation (CV), and 90% CIs.

In order to evaluate the association between the HPT and PK parameters, HPT parameters will be plotted separately for fixed puffing and *ad libitum* use against the PK parameters with study product indicated using different symbols for each nicotine concentration level.

In order to evaluate the association between the theoretical nicotine exposure and PK parameters, theoretical nicotine exposure will be plotted separately for fixed puffing and *ad libitum* use against the PK parameters with product indicated using different symbols for each nicotine concentration level.

Safety analysis:

The safety population will comprise all enrolled subjects. Adverse events will serve for the primary assessment of safety data. All safety data will be listed however only P4M3 variants-emergent AEs will be summarized by product variant (fixed puffing regimen and *ad libitum* use will be combined at the product variant level) and P4M3 overall. Other safety measurements (vital signs, etc.) will be summarized per fixed puffing regimen/*ad libitum* use and product.

Sample Size:

The sample size is empirically based, as there is no prior information on which to base the sample size and there is no consideration for statistical hypothesis. A sample of 12 subjects is targeted for the analysis of this study to obtain the precision about the mean and variance for the study objectives. Therefore, in order to ensure 12 subjects completing the study, 16 subjects will be randomized.

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LIST OF ABBREVIATIONS AND EXPLANATION OF TERMS

Abbreviations

Adapted mCEQ	Adapted version of the modified Cigarette Evaluation Questionnaire
AE(s)	Adverse event(s)
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate transaminase
ATS	American Thoracic Society
AUC	Area under the concentration time curve
$AUC_{(0\text{-}4h)}$	Area under the concentration-time curve from T0 to 4 hours
BMI	Body mass index
$cAUC_{(0\text{-}4h)}$	Background-corrected area under the concentration-time curve that is above the corrected baseline from T0 to 4 hours for the fixed puffing regimen
$cAUCb_{(0\text{-}4h)}$	Background-corrected area under the concentration-time curve that is above the corrected baseline from T0 to 4 hours for the *ad libitum* use
CC(s)	Conventional cigarette(s)
$cC_{average}$	Adjusted average of plasma nicotine concentrations during *ad libitum* use
cC_{max}	Adjusted maximum concentration
cC_{peak}	Adjusted highest plasma concentration during *ad libitum* use
CD	Compact disc
CI	Confidence interval
CIOMS	The Council for International Organizations of Medical Sciences
$C_{average}$	Average of plasma concentrations during *ad libitum* use
C_{max}	Maximum concentration
C_{peak}	Highest plasma concentration during *ad libitum* use
C_{trough}	Lowest plasma concentration after T0 during *ad libitum* use
CO	Carbon monoxide
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CRF	Case report form
CRO	Contract Research Organization
CSR	Clinical Study Report

CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CTMS	Clinical Trial Management System
CV (%)	Coefficient of variation (%)
CV (documentation)	Curriculum vitae
CYP2A6	Cytochrome P450 2A6
DVD	Digital video disc
e-cigarette	Electronic cigarette
ECG	Electrocardiogram
EOS	End of Study
EU	European Union
FDA	US Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HPHC	Harmful and Potentially Harmful Constituents
HPT	Human puffing topography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
ISO	International Organization for Standardization
IU	International units
LA	Lactic acid
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
LSM	Least-squares means
mg	milligram
mL	Milliliter

MedDRA	Medical Dictionary for Regulatory Activities
MRTP	Modified risk tobacco product
ms	Millisecond
n	Number of subjects
NCA	Non-compartmental analysis
ng	Nanogram
NHANES III	National Health and Nutrition Survey III
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMI	Philip Morris International
PPM	Parts per million
QTcB	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, using Bazett's formula
QTcF	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, using Fridericia's formula
RCF	Relative centrifugal force
RRP	Reduced-Risk Product
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SHM	Sample handling manual
SMP	Safety management plan
SOP	Standard Operating Procedure
SQ	Sensory questionnaire
T	Time point
T0	Time point of first product use during study day
$t_{½}$	Half-life
t_{max}	Time to maximum concentration
t_{peak}	Time to peak plasma nicotine concentration
UBC	United BioSource Corporation
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
USB	Universal serial bus

VAS	Visual Analogue Scale
WBC	White blood cell (count)
WHO	World Health Organization
µg	Microgram

Explanation of Terms

The following special terms are used in this protocol:

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

1 ETHICS AND REGULATIONS

1.1 Institutional Review Board (IRB) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (ICF, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's Brochure [IB], available safety information, the Investigator's curriculum vitae [CV] and/or other evidence of qualifications and any other documents requested by an Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IRB. The IRB shall be appropriately constituted and perform its functions in accordance with the International Council for Harmonisation (ICH) Tripartite Guidance for Good Clinical Practice (GCP) and local requirements, as applicable.

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

The written approval from the IRB will be filed in the 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 an investigational site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB.

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

These requirements for approval should in no way prevent any action from being taken by the Investigator or by the Sponsor in order to eliminate immediate hazards to the subjects. If such a change to the protocol is felt to be necessary by the Investigator, and is implemented for safety reasons, the Sponsor and the IRB should be informed immediately.

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

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, 2013 and are consistent with ICH/GCP principles.

The Investigator agrees to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IRB. The Investigator and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki, 2013 should be located in the Investigator's Study File.

1.3 Subject Information and Consent

1.3.1 Study Consent

At the Screening Visit, the Investigator or person designated by the Investigator 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 Investigator or the designee 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 discontinue his/her participation at any time. Once the subject has received all necessary information, and if he/she agrees to participate, this will be documented in the ICF by the date, time, and signature of both the subject and the person who conducted the informed consent discussion. No study-specific procedures will be performed before the ICF has been signed.

The original, dated, and signed ICF(s) must be kept in the Investigator study file at the investigational site, and a copy must be given to the subject.

If a protocol amendment is required, or if new information regarding the risk profile of the IP becomes available, an amendment to the ICF may be required. If revision of the ICF is necessary, the Investigator will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IRB before subjects are required to re-sign the ICF.

The subject will be informed that additional data analyses not mentioned in the protocol or the statistical analysis plan might be performed with the collected data at a later time. If any additional analyses will be performed, they will fully be covered by data confidentiality, as for the main analyses described in this protocol.

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, and Investigator abide by the principles of the ICH guidelines on GCP for pharmaceutical products. These guidelines do not apply to consumer products as they are specifically intended for pharmaceutical products but nevertheless provide a robust and ethical framework for conducting clinical studies with non-therapeutic products such as the test products in this study. Use of terms herein that are typically applied to the evaluation of pharmaceutical products does not imply that the test products evaluated in this study are therapeutic products, i.e., pharmaceutical products, medical devices or combination products

In addition, the Investigator will carry out the clinical study in accordance with applicable national and local laws of the pertinent regulatory authorities.

2 INTRODUCTION

2.1 Background

2.1.1 Study Background

Smoking cessation is the best way for smokers to reduce the risk of developing pulmonary, cardiovascular and other tobacco-related diseases [McEwen *et al,* 2016]. The development of "reduced risk products" with the potential to reduce individual risk and population harm represents an approach to reducing tobacco-related deaths and diseases, particularly among tobacco users who are unwilling to quit smoking [Health Canada, 1999].

Philip Morris International (PMI) is developing and scientifically substantiating Reduced-Risk Products (RRPs), which have the potential to reduce individual risk and population harm in comparison to smoking cigarettes. Such RRPs target to substantially reduce or eliminate the exposure to harmful and potentially harmful constituents (HPHCs), while providing an acceptable option to smokers as substitutes for cigarettes. One of these reduced risk products is the nicotine aerosol delivering system P4M3. P4M3 is an e-cigarette, which is based on the principle of heating a mixture of water, propylene glycol, glycerol, flavor and nicotine (e-liquid) to generate a nicotine-containing aerosol which could satisfy smokers not only in terms of nicotine delivery similarly to that of cigarette but also in terms of taste, sensory experience and ritual. P4M3 is available in two versions: e-liquid containing nicotine and e-liquid containing nicotine and lactic acid. Lactic acid is a weak acid which potentially reduces the perceived harshness of nicotine.

It is widely recognized that the newer-generations of e-cigarettes have become more efficient in delivering nicotine compared to earlier generation products but still fail to appeal to smokers in terms of the speed of nicotine delivery compared to conventional cigarettes [Farsalinos *et al*, 2014]. Electronic cigarette models deliver variable amounts of nicotine to the aerosol which is not directly related to the nicotine content in the liquid [Goniewicz *et al*, 2014]. A number of studies have evaluated nicotine in e-cigarettes aerosol generated by smoking machines.

Significant inter-subject variability has been described for HPT parameters, especially puff duration, puff frequency, and flow rate [Robinson *et al*, 2015]. Experienced e-cigarette users may extract more nicotine by drawing relatively low velocity, long duration puffs in comparison to conventional tobacco cigarette smokers. E-cigarette design features also affect nicotine exposure; increasing the battery voltage output and e-liquid nicotine concentration increases the nicotine delivery [Talih *et al*, 2015]. The correlation between nicotine in the e-liquid and in the aerosol is low, because the 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. Additionally, the individual puffing style and preference generate yet another key determinant of nicotine delivery to users [Mcneill *et al*, 2015]. Published data describe that 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 [Farsalinos *et al*, 2015]. Therefore, it is reasonable to assume that speed and amount of nicotine absorption is not solely related to concentration of nicotine in the e-liquid.

2.1.2 Description of the Product and Scientific Findings

PMI is developing the nicotine aerosol delivering system, P4M3. P4M3 is an e-cigarette, which is based on the principle of heating a mixture of propylene glycol, glycerol, water, tobacco-derived nicotine, and flavors, with or without lactic acid (e-liquid) to generate a nicotine-containing aerosol.

P4M3 is a puff-activated battery-powered device which produces a visible and inhalable aerosol. P4M3 system has three distinct components, which perform different functions during product use:

- A Battery (and electronics) Unit, onto which the Cartomizer is mounted.
- A disposable Cartomizer, which contains porous materials, a heater, and the nicotine solution (e-liquid).
- A USB cable to charge the Battery unit from a low voltage port.

Please refer to the IB for non-clinical findings.

2.2 Purpose of the Study

The goal of the study will be to evaluate the nicotine concentration profiles and derived PK parameters, subjective and behavioral effects, and puffing topography parameters of P4M3 with four liquids of various nicotine concentrations with and without lactic acid (ranging from 1.7% to 4%) in experienced e-cigarette users following a single-use experience with fixed puffing and after *ad libitum* use of P4M3. Four (4) variants of P4M3 with incremental nicotine concentrations ranging from 1.7% (with and without lactic acid) to 4% (with lactic acid) will be evaluated together with subjects' own e-cigarettes to evaluate the relationship between the e-liquid composition (nicotine concentrations and presence of lactic acid) and the amount of nicotine absorbed, the speed of absorption, and the puffing topography. Furthermore, the associations between the PK parameters and human puffing topography parameters following a fixed puffing and *ad libitum* use will be evaluated. Additionally, subjective effects and related behavior will be assessed by the means of questionnaires, to provide further insights on product acceptance. Ultimately, the goal of this study is to select the variant(s) that result(s) in nicotine absorption close to that observed with subjects' own e-cigarettes.

Safety will also be assessed throughout the study.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

All subjects will be under medical supervision during the entire study to monitor for any potential nicotine overexposure.

Nicotine abstinence support will be performed as required during the study. The nicotine concentrations tested in this study are used in currently marketed electronic cigarettes.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

- Risks related to blood sampling, e.g., excessive bleeding, fainting, hematoma, paraesthesia, or infection.

- Risks related to drug application as part of testing procedures (i.e., spirometry with short-acting bronchodilator at Screening) per study protocol and scientifically accepted standards.

- The risk of procedures (e.g., blood drawing, spirometry) are deemed to be on a par with procedures routinely performed during normal or extended health examinations by the subject's healthcare professional. The total volume of blood planned to be drawn is approximately 434 mL and does not exceed the levels for a standard blood donation.

- Change in product use habits due to study requirements and related concomitant symptoms, e.g., craving, nicotine withdrawal symptoms.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product (P4M3)

All risks related to study procedures, IP, or support for nicotine abstinence will be explained in detail to the subjects. Mitigation will include, but will not be limited to:

- Close monitoring and medical evaluation of potential safety signals throughout the study and passive safety FU.

- Using accepted research and scientific standards e.g., blood samples not to exceed blood donation standards.

- Management and follow-up of AEs/SAEs.

2.3.4 Unforeseeable Risks

As with the use of any IP, there may be unforeseeable risks and hazards that could occur. The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety.

Tobacco and nicotine withdrawal symptoms are common in smokers. The possibility of withdrawal symptoms will be explained at Screening, Day -1 (Baseline), and Day of Discharge. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest possibility.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective and Endpoints

Primary Objective and Endpoints

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

Endpoints:

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

3.2 Secondary Objectives and Endpoints

Secondary Objectives and Endpoints

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

Endpoints:

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

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

Endpoints:

- Product evaluation by Adapted mCEQ (60 minutes *ad libitum* use only)
- VAS for craving (fixed puffing and 60 minutes *ad libitum* use)
- Adapted SQ (fixed puffing and 60 minutes *ad libitum* use)

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

Endpoint:

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

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

Endpoints:

- Theoretical nicotine exposure calculated as total puff volume [mL] (from HPT) x nicotine [µg/mL] (deriving the nicotine [µg/mL] from the CORESTA regimen to determine the nicotine [µg] per puff [55 mL]) for each of the P4M3 variants.
- cC_{peak} - cC_{trough} versus theoretical rate of nicotine inhalation (R_0) (60 minutes *ad libitum* use only)
- $cAUCb_{(0\text{-}4h)}$ versus theoretical nicotine exposure (60 minutes *ad libitum* use only)
- cC_{max} versus theoretical rate of nicotine inhalation (R_0) (fixed puffing regimen only)
- $cAUC_{(0\text{-}4h)}$ versus theoretical nicotine exposure (fixed puffing regimen only)

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

Endpoints:

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

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

Endpoint:

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

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

Endpoints:

- Incidence of AEs and SAEs
- Frequency of AEs and SAEs

- Incidence of P4M3 device events including malfunction/misuse
- Physical examination changes from baseline
- Changes from baseline of VAS, three Likert scales and the open question of Cough assessment questionnaire
- ECG changes from baseline (heart rate, PR, QRS, QT, QTcB , QTcF intervals)
- Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Spirometry changes from baseline (FEV_1, FEV_1 % predicted, FVC, FEV_1/FVC)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel (described in Table 2)
- Concomitant medications

3.3 Study Hypothesis

There are no statistical hypotheses to be tested.

3.4 Exploratory Endpoints

There are no exploratory analyses planned.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a single-center, open-label, concentration-ranging study to evaluate the nicotine PK profile and PD effects in healthy White adult experienced users of closed tank/cartridge e-cigarettes using four different variants of P4M3 or their own e-cigarettes.

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

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

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

- a fixed puffing regimen comprising of 12 puffs in total at a rate of one puff every 30 seconds (± 5 seconds) with HPT recording in the morning.
- *ad libitum* use for 60 minutes (± 5 minutes) with HPT recording in the afternoon

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

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

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

Sequence 1:

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

Sequence 2:

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

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

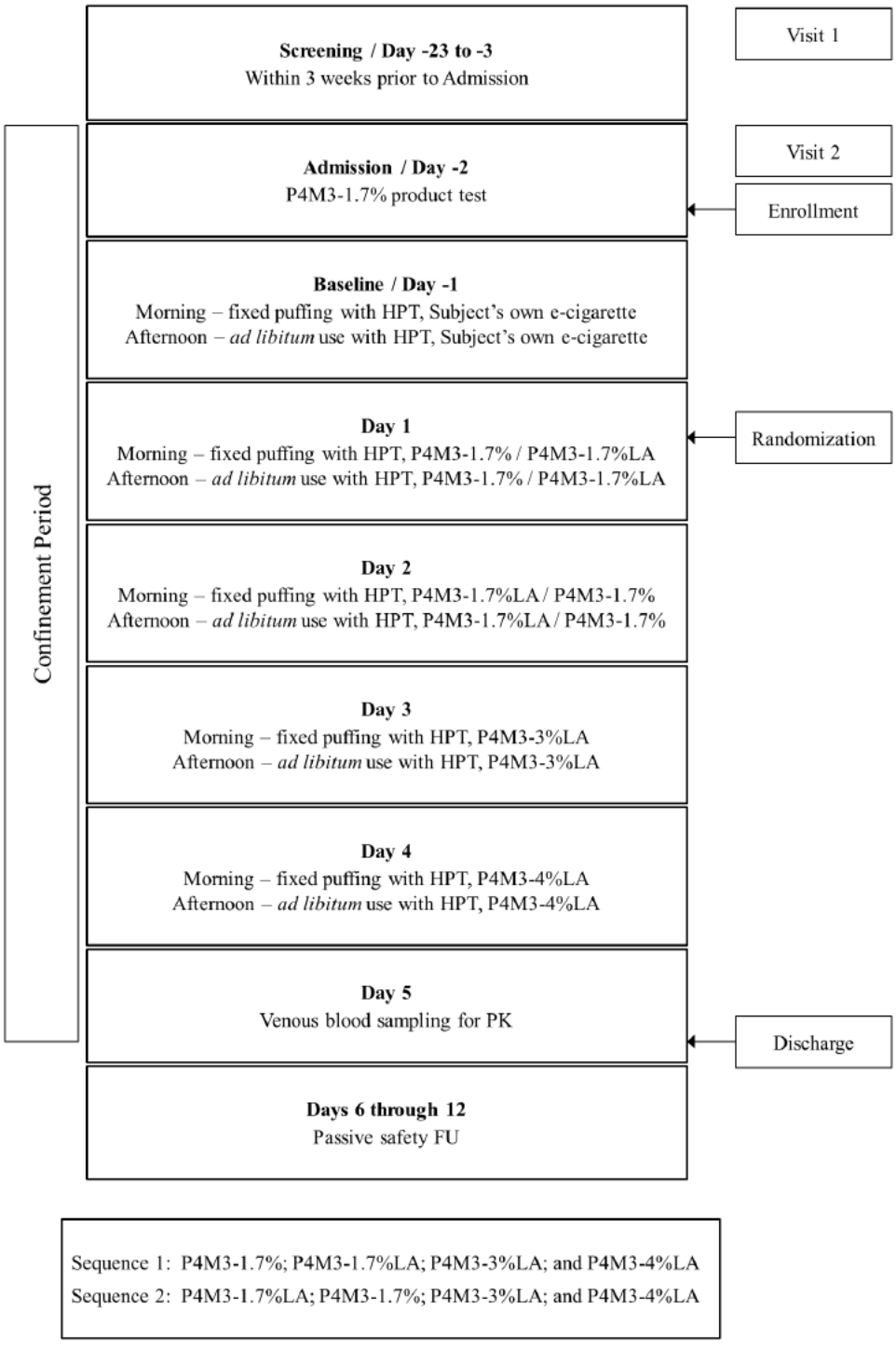
Venous blood samples will be taken for analysis of PK parameters prior to the start of and during both fixed puffing and the 60 minutes *ad libitum* use at specified time points before and after T0 on Day -1 to Day 4. Blood sampling for the determination of nicotine and derived PK parameters will be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

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

Subjects will be discharged following completion of assessments at Day 5 and will enter a 7-day passive safety FU during which there will be recording of spontaneously reported new AE/SAEs and the active follow-up of ongoing AE/SAEs by the Investigator. Any non-serious AE that is ongoing during the passive safety FU will be actively followed up by the Investigator or designee during that period until it has been resolved, stabilized (i.e., no worsening of the condition), an acceptable explanation has been found (e.g., a chronic condition) or lost to follow-up. At the end of the passive safety FU, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for them anymore by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly. All SAEs will be followed up by the Investigator or designee, despite their continuation after the end of the passive safety FU, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). SAEs reported after the subject's EOS that are considered related to P4M3 by the Investigator must be captured and reported to UBC/PMI regardless of time after EOS. The EOS for a subject is defined as his/her discharge on Day 5 or the date of early termination of the subject, plus 7 days of passive safety FU.

The study schematic is presented in Figure 1. The schedule of events is provided in Appendix 1.

Figure 1 Study Schematic



4.2 Rationale for Study Design

The goal of the study will be to select the P4M3 variant(s) that result(s) in nicotine absorption close to that observed with subjects' own e-cigarettes. The nicotine plasma concentration profiles and derived PK parameters, subjective and behavioral effects, and HPT parameters of P4M3 variants and subjects' own e-cigarettes will be evaluated. The concentrations of nicotine in some of the P4M3 variants tested in this study are already available on the market and exposure of the IPs will be to experienced e-cigarette users aged 21 - 65 years (inclusive) following a single-use experience with fixed puffing in the morning and after *ad libitum* use of P4M3 in the afternoon across 4 days. Subjects with a history of e-cigarette use were chosen for this study based on data from previous studies indicating that having previous experience using such products may impact nicotine exposure and puffing topography (Farsalinos 2013, 2015; Spindle 2015). Further, the use of fixed and *ad libitum* puffing regimens by experienced consumers is expected to provide insight into nicotine delivery by the products that is possible under consistent use conditions across subjects (fixed puffing regimen) as well as a means to assess the products' ability to meet a consumers needs during short-term "real-life" use conditions (*ad libitum* regimen).

Plasma nicotine presents a biphasic profile, with a typical rapid initial disposition half-life ($t_{1/2\alpha}$) of 1.35 hours, followed by a slower terminal elimination half-life ($t_{1/2z}$) of 17 hours (Marchand et al, 2017). To ensure a full nicotine washout between each product use, a separation of 3 days would be required (~ 5 x elimination $t_{1/2z}$). Due to the impracticality of undergoing long periods of abstinence for smokers, shorter washout periods have been selected. To minimize the potential bias in the nicotine plasma PK parameters for the fixed puffing regimens, background-concentration correction will be applied to adjust for carry-over effects. The simplest approach by which this can be achieved requires a) a minimum washout-out period of 10 hours prior to each fixed puffing regimen session (this ensures that subjects have entered the terminal elimination phase of nicotine) and b) the estimation of $t_{1/2z}$ (or the terminal elimination rate constant λ_z) on Day 5 for each subject.

The use of estrogen-containing contraceptives is known to accelerate nicotine clearance by 20% to 30% in women as compared to women who do not take such contraceptives (Benowitz *et al*, 2006). Therefore, for the purpose of this study, it is not allowed to use hormonal contraception containing estrogen or hormone replacement therapy.

The activity of CYP2A6 will be measured at Admission as nicotine metabolism by CYP2A6 varies between individuals of the same ethnicity/race, and across ethnicity/race due to genetic variations. These genetic differences could be associated with reduced/increased nicotine metabolism (Hukkanen *et al*, 2005).

4.3 Study Duration

The entire study per subject will last between 15 to 36 days, including a Screening Visit of up to 3 weeks (Day -23 to Day -3) prior to Admission, 1 day of Admission (Day -2), 5 days of product use (Days -1 to 4), and 7 days of passive safety FU.

4.4 Appropriateness of Measurement

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

All questionnaires to be used during the study, with the exception of the cough questionnaire, are adapted versions of validated questionnaires.

4.5 Study Stopping Criteria

The study may be stopped if the subjects are placed at risk because of clinically significant findings or SAEs that, e.g.:

- are assessed as causally related to P4M3.
- are not considered to be consistent with continuation of the study
- are not consistent with the information provided in Section 6.5 of the current IB

The Sponsor, Investigator, and/or IRB reserve the right to terminate or suspend the study at any time; however this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the case report forms (CRFs). The Investigator should notify the IRB in writing of the study's completion or early discontinuation.

In the event that the study is terminated early, every effort should be made by the Investigator, investigational site personnel, and Sponsor to follow AEs and SAEs for all subjects until the end of the passive safety FU.

5 STUDY POPULATION

5.1 Selection of Study Population

Sixteen (16) White female or male healthy adult subjects who have used e-cigarettes daily for at least 3 months prior to the Screening Visit will be enrolled into this study. The e-cigarette use status of the subjects will be verified based on a urine cotinine test (cotinine ≥ 200 ng/mL).

5.1.1 Inclusion Criteria

Inclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
1. Subject has signed the ICF and is able to understand the information provided in the ICF.	Administrative	X	
2. Subject is aged from 21 to 65 years, inclusive, at the Screening Visit.	Safety	X	
3. Subject is White.	Effect	X	
4. Subject is a former daily cigarette smoker who smoked at least 100 cigarettes or more in his/her life and ceased smoking at least 3months prior to the Screening Visit.	Safety	X	
5. Subject has been using a commercially available, nicotine-containing closed tank/cartridge e-cigarette daily for at least 3 months prior to the Screening Visit.	Effect	X	
6. Subject has a urine cotinine test ≥200 ng/mL at the Screening Visit and Admission.	Effect	X	X
7. Subject does not plan to quit using e-cigarettes during the study.	Effect	X	X
8. Subject is ready to comply with study procedures.	Effect	X	X

Inclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
9. Subject is ready to accept periods of interruption of nicotine use.	Effect	X	X
10. Subject is ready to accept using the P4M3 product variants as instructed and for the duration of the study.	Effect	X	X

5.1.2 Exclusion Criteria

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

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
1. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition (including safety laboratory as per CTCAE), which as per the judgment of the Investigator would jeopardize the safety of the subject).	Safety	X	X
2. Subject has abnormal renal function test result or subject with a creatinine clearance <60 mL/minute (as determined by the Cockcroft-Gault) at the Screening Visit, confirmed on repeat testing.	Safety	X	
3. Subject has elevated liver function test results (ALT or AST >2X ULN) at the Screening Visit.	Safety	X	

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
4. Subject has bilirubin >1.5X ULN (isolated bilirubin >1.5X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at the Screening Visit.	Safety	X	
5. Subject has FEV_1/FVC <0.7 and FEV_1 <80% predicted value at post-bronchodilator spirometry at the Screening Visit.	Safety	X	
6. Subject has asthma condition (FEV_1/FVC <0.75 and reversibility in FEV_1 >12% and > 200 mL from pre- to post-bronchodilator values) at the Screening Visit.	Safety	X	
7. Subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug (whichever is longer) prior to Admission which has an impact on CYP2A6 activity (See Table 1).	Safety		X
8. Subject has a CO breath test ≥ 10 ppm at the Screening Visit or Admission.	Effect	X	X
9. Subject has a positive alcohol test at the Screening Visit or Admission and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in study.	Administrative	X	X
10. Subject has a positive urine drug screen at the Screening Visit or Admission.	Administrative	X	X
11. Subject has a BMI <18.5 kg/m^2 or BMI ≥35 kg/m^2 at the Screening Visit.	Safety	X	

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
12. Subject has a positive serology test for HIV 1/2, hepatitis B, or hepatitis C at the Screening Visit.	Administrative	X	
13. The subject has a baseline QTcF >450 ms for males or >470 ms for females at the Screening Visit or history of congenital long QT syndrome, or Torsades de Pointes.	Safety	X	
14. Subject has abnormal (clinically significant) ECG findings at the Screening Visit. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by the Investigator.	Safety	X	
15. Subject or one of their family members* is a current or former employee of the tobacco industry.	Administrative	X	
16. Subject or one of their family members* is an employee of the investigational site or any other parties involved in the study.	Administrative	X	
17. Subject has participated in a clinical study within 3 months prior to the Screening Visit.	Safety	X	
18. Subject has been previously screened in this study and failed to meet the eligibility criteria.	Administrative	X	

Exclusion Criteria	Rationale	Screening	Day of Admission (Day -2)
19. Subject smokes combustible cigarettes or other tobacco products (with the exception of commercially available, nicotine containing closed tank/cartridge e-cigarette).	Effect	X	X
20. Subject is using estrogen-containing medication.	Effect	X	X
21. Female subject of childbearing potential who is pregnant or breastfeeding.	Safety	X	X
22. Female subject of childbearing potential who does not agree to use an acceptable method of effective contraception**. Female subject who is not of childbearing potential must meet at least one of the following criteria: - has undergone hysterectomy or bilateral tubal ligation, - has medically confirmed ovarian failure, or - is medically confirmed to be postmenopausal (cessation of regular menses for at least 12 consecutive months prior to Admission with no alternative pathological or physiological cause).	Safety	X	X

* As defined by the FDA guidance 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"

**Acceptable methods of effective contraception:

Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from the Screening Visit until the end of the passive safety FU. Hormonal contraception with estrogen containing products is NOT allowed in this study.

5.1.3 Discontinuation of Subjects from the Study

Subjects will be informed that they are free to withdraw from the study at any time. Subjects should be questioned for the reason of premature withdrawal, although they are not obliged to disclose it. This needs to be fully documented in source documents and reported in the CRF.

When a subject is discontinued (withdraws or is discontinued) from the study, the early termination procedure planned (Section 9) must be performed as soon as possible after the time of discontinuation unless subject withdrew the informed consent to do so. After the time of discontinuation, the subject will enter into a 7-day passive safety FU. Subjects withdrawn or discontinued from the study cannot re-enter the study.

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

- Withdrawal of informed consent.
- Any AE or condition (including clinically relevant changes in a laboratory parameter) at the discretion of the Investigator.
- Positive pregnancy testing (no invasive procedures including the drawing of blood must be performed after detection of pregnancy, see Section 8.5).
- Female subjects starting contraception or hormone replacement therapy containing estrogens during the study.
- The use of any nicotine/tobacco product which is different from the assigned IP.
- The Sponsor or Investigator terminates the study.
- Discontinuation is considered to be in the best interest of the subject or the other subjects.

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

- Lost to follow-up.
- Non-authorized concomitant medication as defined in the context of this study (in general, any concomitant medication should be discussed with the Contract Research Organization [CRO] Medical Monitor on an ongoing basis).
- Non-compliance to the study procedures.

Subjects discontinued after randomization will not be replaced and will not be allowed to re-enter. All withdrawals and discontinuations have to be documented properly in the CRF.

5.1.4 Violation of Selection Criteria

Subjects who are eligible at the Screening Visit but who do not meet the entry criteria at Admission (Day -2) prior to enrollment will be considered a screening failure.

6 INVESTIGATIONAL PRODUCTS

6.1 P4M3

6.1.1 Description

The P4M3 will be provided by the Sponsor and its distribution will be controlled by a qualified and appropriately trained designee. P4M3 with e-liquid contains the following concentrations of nicotine with and without lactic acid: 1.7 % nicotine without lactic acid, 1.7 % nicotine with lactic acid, 3 % nicotine with lactic acid, and 4 % nicotine with lactic acid.

P4M3 comprises the following components:

- A Battery (and electronics) Unit, onto which the Cartomizer is mounted.
- A disposable Cartomizer, which contains porous materials, a heater, and the nicotine solution (e-liquid).
- A USB cable to charge the Battery unit from a low voltage port.

6.1.2 Packaging and Labelling

The P4M3 variants will be packaged and labelled appropriately for in-clinic subject use during the study.

6.2 Subjects' Own e-Cigarettes

6.2.1 Description

Subjects will bring their own e-cigarette with e-liquid. Subjects' own e-cigarettes have to be commercially available, closed tank/cartridge e-cigarette. Subject will be asked to buy the anticipated amount of e-cigarette (e-liquid) for the study.

6.3 Use of Investigational Products

Subjects will never be forced to use the products and will be free to stop using the products at any time during the study. Subjects caught using any nicotine/tobacco product which is different from the assigned IP will be discontinued from the study. During the screening period, subjects will be allowed to use e-cigarettes according to their usual habits except during the procedures of the Screening Visit.

6.3.1 Admission (Day -2)

Subjects will be admitted to the investigational site at Admission (Day -2) for assessments and a debriefing on P4M3. Subjects should have been fasting for at least 12 hours prior to Admission. After confirmation of subjects' eligibility, subjects will be enrolled in the study, have a debriefing on

P4M3, and perform a product test with P4M3-1.7% for a maximum of 10 minutes. The product test will be physically connected to the puffing topography device without recording of parameters (HPT device switched off). After the product test, subjects not willing and/or ready to use P4M3 will be discontinued and may be replaced. Following the product test, subjects will be required to abstain from any nicotine/tobacco containing product use for at least 10 hours until the first product use on Day -1.

6.3.2 Baseline (Day -1)

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

6.3.3 Investigational Period (Day 1 to Day 5)

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

Sequence 1:
P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA

Sequence 2:
P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA

On Days 1 to 4, subjects will be provided and instructed to use a new, ready-to-use product (full cartridge) of the assigned P4M3 variant for fixed puffing regimen with HPT recording in the morning and another new one for the *ad libitum* use for 60 minutes with HPT recording in the afternoon, according to one of two randomly assigned sequences. The concentration of P4M3 e-liquid will be the same on a given day for fixed puffing and *ad libitum* use on Days 1 to 4. T0 for 60 minutes *ad libitum* use should be at least 10 hours after T0 for fixed puffing to allow adequate characterization of nicotine plasma AUCs. There will be a washout of at least 10 hours following each *ad libitum* product use with respect to the subsequent fixed puffing regimen in the next morning to allow adequate background correction of the fixed puffing regimen-related nicotine plasma concentrations.

Following product use on each day, the used e-liquid cartridges will be collected for assessment of e-liquid use. E-liquid cartridges will be weighed prior and post product use.

Except for the test products, subjects will not be allowed to use any nicotine-containing products through Discharge or early termination.

Subjects will be continuously supervised during P4M3 usage.

6.3.4 Safety Period

During the passive safety FU period, subjects are free to use e-cigarettes according to their usual habits.

6.3.5 Stopping Rules for Investigational Product

For safety purposes, use of the IPs should be temporarily reduced or stopped in the event of any signs suggesting nicotine overexposure, e.g., gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach, 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).

6.4 Method for Assigning Subjects to Study Arms

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

Sequence 1:
P4M3-1.7%; P4M3-1.7%LA; P4M3-3 %LA; and P4M3-4%LA

Sequence 2:
P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA

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

6.5 Blinding

This is an open-label study; however the site (except the pharmacy staff preparing the IPs for administration) will be blinded to the randomization sequences until they are assigned. Subjects will not be informed of the complete sequence to which they have been assigned to receive the P4M3 products.

6.6 Investigational Product Accountability and Compliance

6.6.1 Dispensing Investigational Products

From Day -2 until Day 4, P4M3 device and cartomizer will be dispensed, ready-to-use, by the Investigator or dedicated study staff, as per study design. Each dispense of the IP will be recorded in a log. The log should include subject number, date, and start and stop time of product use. The product will not be promoted for commercial distribution or test market.

Subjects will bring a sufficient quantity of their own e-cigarettes and e-liquids before or at the time of Admission on Day -2, which will be collected by dedicated study staff, labeled with subject number, and stored. The Investigator or dedicated study staff will dispense the subject's own e-cigarette and e-liquid as per study design. Each dispense of the IP will be recorded in a log. The log should include subject number, date, and start and stop time of product use.

6.6.2 Storage and Accountability

The P4M3 device and cartomizer will be stored in a secured storage place at the investigational site with access limited to the authorized personnel only. Full accountability of the distributed products will be ensured by designated staff. Subjects will return the P4M3 device and cartomizer immediately after use to the investigational site personnel for accountability. This will be documented in an appropriate log.

6.6.3 Investigational Product Retention

The P4M3 devices and cartomizers (dispensed and non-dispensed) will be returned to the Sponsor upon study completion.

6.6.4 Compliance to Investigational Products

Compliance will be ensured by strict distribution of the products (product by product) and collection of used P4M3 devices and cartomizers and used subjects' own e-cigarettes after each product use will be documented in appropriate logs.

6.7 Restrictions

6.7.1 Nicotine/Tobacco Product Restrictions

Subjects will not be allowed to use any nicotine/tobacco-containing products except their own closed tank/cartridge e-cigarette on Day -1 and the P4M3 test products as required per protocol from Days 1 to 4 through Discharge on Day 5 or early termination.

6.7.2 Dietary and Activity 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 in order to avoid a "high-fat" diet. A "high-fat" diet is 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) (FDA, 2002).

Subjects should refrain from ingesting foods or beverages containing grapefruit or seville-type (sour) oranges and marmalade, apple, orange, pineapple, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats from 7 days prior to Day -2 and throughout the study.

Subjects are not allowed to bring their own food or beverages to the investigational site. Water, light snacks, fruits, and raw vegetables can be distributed to the subjects without restrictions at any time during confinement as long as they comply with the dietician's standard diet. Consumption of food or beverage (including water) will not be allowed during each product use on Day -1 to Day 4. The same menu and meal schedule will be administered uniformly for all subjects. Fasting state has to be observed for at least 12 hours prior to blood drawings for the safety laboratory on Day -2, Day 2, and Day 5.

Subjects should refrain from strenuous and/or unaccustomed exercise throughout the entire course of the study.

6.8 Concomitant Medication

Concomitant medication will first be assessed at the Screening Visit. Concomitant medication taken by the subject 4 weeks prior to the Screening Visit will be captured.

Medication supportive for smoking abstinence will not be allowed (e.g., varenicline).

In this study, the use of hormonal contraception containing estrogens is NOT allowed. This also applies to hormone replacement therapy. Only hormonal contraception with products containing progesterone is allowed during this study. Subjects using estrogens during the study will be discontinued.

To be eligible for the study any medication with impact on CYP2A6 metabolism must be discontinued at least 14 days prior to admission to the investigational site or for at least 5 half-lives (whichever is longer). They must not be used during the entire study until the time of discharge or early termination.

The following drugs and substances are considered as having an impact on CYP2A6 activity (American Pharmacists Association. Drug Information Handbook, 23rd edition, 2014; Table 1). Prior to database close, the concomitant medications will be assessed according to the potential impact on CYP2A6 activity and the potential impact on study results.

Table 1. CYP2A6: Substrates, Inhibitors, and Inducers

Inhibitor	Drug Class
Amiodarone	Antiarrhythmic agent, Class III
Desipramine	Antidepressant
Isoniazid	Anti-bacterial drug
Ketoconazole	Anti-fungal medication
Letrozole	Anti-estrogen drug
Methoxsalen	Systemic psoralens
Miconazole	Anti-fungal medication
Tranylcypromine	Antidepressant
Inducer	**Drug Class**
Amobarbital	Barbiturate
Pentobarbital	Barbiturates
Phenobarbital	Barbiturates/anticonvulsa
Rifampin	Antimycobacterials
Secobarbital	Barbiturates
Substrate	**Drug Class**
Dexmedetomidine	α_2-Adrenoceptor, sedative
Ifosfamide	Anti-cancer, alkylating agents

American Pharmacists Association. Drug Information Handbook, 2014. 23rd edition, Cytochrome P450 enzymes: substrates, inhibitors, and inducers. p. 2316-24.

However, the Investigator is responsible for the medical care of the subjects during their participation in this study. Any decisions regarding the prescription of medication will be taken in the best interest of the subject.

If the use of a concomitant medication cannot be avoided for the subject's safety it has to be fully documented (for details, see Section 7.3.5). Concomitant medications should be followed up with the CRO Medical Monitor on an ongoing basis.

Use of any concomitant medication should be discussed with the CRO Medical Monitor. It is at the discretion of the Investigator in agreement with the Sponsor to assess if a termination of such medication at Screening is medically justified and safe for the subject.

7 STUDY PROCEDURES

Personnel performing study measurements or recordings must have the appropriate training fully documented. Quality and control measures have to be in place. All study procedures are provided as an overview in the Schedule of Events (Appendix 1). In this section, only the expected/planned time points for the various measurements are given. Considering that not all subjects can have a procedure at the same time point, adequate time windows will be given for each study procedure and each time point. Investigational site personnel will adhere to their Standard Operating Procedures (SOPs) for all activities. Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care.

7.1 Informed Consent

Each subject must give his/her informed consent prior to participating in the study (i.e., at the Screening Visit). During the consent process, the Investigator or designee obtaining consent must inform each subject of the nature, risks, and benefits of, and alternatives to study participation. In addition, each subject must review the subject information provided within the ICF and must have sufficient time to read and understand and have adequate opportunity to ask questions. The ICF must be signed, dated, and timed prior to undertaking any study-specific procedures. A signed copy must be given to the subject.

7.2 Support during Nicotine Abstinence

All subjects will be closely monitored by the investigational site personnel. This includes monitoring of clinical tests e.g., vital signs, physical examination, and body weight. It also refers to close monitoring of the subject's behavior, AEs, and his/her mood.

7.3 Clinical Assessments

Any clinically relevant finding detected during the Screening Visit has to be documented as a concomitant disease. This also applies to clinically relevant findings in e.g., laboratory values, vital signs, and ECGs, detected during the Screening Visit. Any untoward medical occurrence in a subject detected during the study which was not present at the Screening Visit must be documented as an AE. Worsening of a pre-existing condition from the Screening Visit onwards will also be documented as an AE. If a clinically relevant finding is detected during the Screening period, the Investigator needs to check that the subject is healthy as judged by the Investigator and based on available assessments (Section 5.1.1).

7.3.1 Demographic Data

Demographic data (sex, date of birth/age, and race) will be recorded on the day of ICF signature.

7.3.2 Identification of the Current Electronic Cigarette Brand

Identification of the current e-cigarette brand used by the subject will be done at the Screening Visit and on Day -2. For the Screening Visit, potential subjects will be asked to bring an e-cigarette of their current brand to the investigational site. The investigational site personnel will take a photograph of the subject's current brand product. Photographs will be considered as Source Documentation. A copy of the photos will be provided to the Sponsor electronically as digital DVD or compact disc (CD).The investigational site personnel will, in addition, document the current brand product of each subject and will document e-cigarette name, nicotine concentration, and device details as appropriate (e.g., generation, power settings, e-liquid source, etc.).

7.3.3 Electronic Cigarette Use and Smoking History

Subjects will be questioned for their e-cigarette use and smoking history by completing a smoking habits questionnaire. At the Screening Visit and on Day -2, this will include questions to evaluate whether the subject has been a former CC smoker of at least 100 cigarettes or more in a lifetime, has not smoked a CC cigarette for at least 3 months prior to the Screening Visit and has been using e-cigarettes (closed tank/cartridge) daily for at least 3 months prior to the Screening Visit. At the Screening Visit only, the subject will also be asked if he/she is planning to quit using his/her own e-cigarettes before completion of the study, i.e., end of passive safety FU. In addition, the subject will be asked if he/she has used nicotine-containing products other than his/her commercially available e-cigarettes, within 3 months prior to the screening assessment.

Furthermore, subjects will be asked if they are ready to accept using the P4M3 product as instructed and for the duration of the study. Only subjects prepared and able to comply with this requirement will be considered for participation in the study.

7.3.4 Demonstration and Product Test of P4M3

All subjects will have a demonstration of the P4M3 by the investigational site personnel at the Screening Visit. On Day -2, following enrollment, subjects will have a product test with P4M3-1.7% *ad libitum* for a maximum of 10 minutes. P4M3-1.7% will be connected to the HPT device without recording of parameters. Only subjects willing and ready to use the P4M3 will continue with the study.

7.3.5 Medical History, Concomitant Disease, Previous and Ongoing Medications

Relevant medical history and any concomitant disease will be documented at the Screening Visit. Medical history is defined as any condition that started prior to and ended prior to the Screening Visit. A concomitant disease is defined as any condition that started after ICF signature or started prior to the Screening Visit and is still ongoing at the Screening Visit.

Any concomitant medication taken within 4 weeks prior to the screening visit needs to be documented. Any medication which was started prior to the Screening Visit and is still being taken by the subject will be considered a concomitant medication. Medication initiated after Screening is also

referred to as concomitant medication. This applies to both prescription and over-the-counter products.

Records should include the drug name (preferably both generic and trade name), route of administration, (e.g., oral, intravenous), total daily dose/unit (expressed in, for example, mg, mL, or IU), indication, the start and, if applicable, the stop date (day, month, and year). Therapy changes (including changes of regimen) during the study are to be documented. If a concomitant medication is still being taken by the subject at the end of the study, this will be recorded on the CRF.

7.3.6 Physical Examination

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

7.3.7 Body Height and Weight

Body height, weight, and BMI will be recorded at the Screening Visit. The BMI will be calculated from the body weight and height using the following formula:

BMI (kg/m^2) = weight in kilograms (kg) / height in meters^2 (m^2).

7.3.8 Vital Signs

Systolic and diastolic blood pressure, pulse rate, and respiratory rate will be measured at the Screening Visit, on Admission (Day -2), and on every day of confinement (Days -1 through 5, pre-product use and 60 minutes [±10 minutes] post end of product use and at Discharge), or at early termination. All parameters will be recorded in the supine position after the subject has rested for at least 5 minutes.

7.3.9 Other Clinical Assessments

7.3.9.1 Spirometry

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

Spirometry will follow the 2005 testing and quality recommendations by the American Thoracic Society/European Respiratory Society Joint Task Force on the standardization of spirometry along with the electronic data submission and documentation processes (American Thoracic Society [ATS], 2005). Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set (Hu and Cassano (NHANES III), 2000).

All personnel performing lung function testing should have the appropriate training and quality control measures should be put into place and be properly documented and filed at the pulmonary function laboratory (including the records of the calibration, if applicable).

The subject will be submitted to a spirometry with maximum voluntary ventilation measurement.

For spirometry, assessed parameters will include:

- FEV_1
- FEV_1 % Predicted
- FVC
- FEV_1/FVC

7.3.9.2 Electrocardiogram

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

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval, corrected by the ECG device according to Bazett's formula and Fridericia's formula. Every ECG has to be assessed as normal, abnormal – clinically not relevant, or abnormal – clinically relevant. A diagnosis has to be provided in the CRF for all ECGs assessed as abnormal – clinically relevant. ECG print-outs will be interpreted by a qualified physician and included in the Source Data File.

7.4 Biomarker Assessment

7.4.1 Biomarkers of Exposure to Nicotine

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

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

A total of 10 blood samples will be taken for fixed puffing PK parameter estimation. One blood samples will be taken prior to the product use (T0) 15 minutes ± 5 minutes (T-1). Thereafter in relation to T0, blood will be drawn at the following time points: T1 after 2 minutes ± 30 seconds, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, and T9 after 4 hours ± 5 minutes.

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

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

c) Day 5 (or Early Termination Visit)

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

The total number of PK samples collected in this study for an individual subject will be 95 over a period of 6 days. The corresponding incurred total blood loss volume for PK is therefore estimated to be approximately 380 mL per subject.

7.4.2 CYP2A6 Activity

CYP2A6 activity will be measured in plasma on Day -2 (Jacob *et al*, 2011~~Jacob *et al*, 2011~~). CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites. In this study the CYP2A6 activity will be measured using the plasma metabolic molar ratio of *trans*-3'-hydroxycotinine/cotinine.

7.5 Laboratory Assessments

A list of laboratories is provided in Appendix 2.

7.5.1 Clinical Chemistry, Hematology, and Urine Analysis for Safety Panel

Hematology, clinical chemistry, and urine analysis for the safety panel will be measured at the Screening Visit, at Admission (Day -2), at Day 2 and at Discharge (Day 5) or early termination. Tests will be conducted at a local laboratory or at the investigational site. Except for the Screening visit, blood will be taken after no less than 12 hours of fasting (see Section 6.7.2). The urine test will be performed semi-quantitatively as urine dip-stick test at the site. Parameters to be measured are listed in Table 2.

Table 2. Clinical Laboratory Parameters for 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 (count) (WBC)
- 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

* Clinical chemistry tests will be performed after at least 12-hour fast from Day -1 assessments; however, in case of dropouts or rechecks, subjects may not have fasted for 12 hours before the clinical chemistry sample is taken.

** At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

7.5.2 Serology

A test for hepatitis B surface antigen, hepatitis C virus, and HIV (anti-HIV1/2 and p24 antigen) will be done at the Screening Visit. In case of positive results, the subject will be referred for appropriate medical care.

7.5.3 Urine Drug Screen

A urine drug screen will be performed at the site at the Screening Visit and at Admission (Day -2). The urine will be screened for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and methadone.

7.5.4 Breath Alcohol Screen

An alcohol screen (breath) will be performed at the site at the Screening Visit and at Admission.

7.5.5 Urine Cotinine Screening

A urine dip-stick cotinine test will be performed at the Screening Visit and at Admission. The test must detect cotinine with a cotinine level of ≥ 200 ng/mL.

7.5.6 Carbon Monoxide Breath Test

A CO breath test will be performed at the Screening Visit and at Admission. Subjects with CO results ≥ 10 ppm will be excluded.

7.5.7 Serum Follicle-Stimulating Hormone Testing

Serum follicle-stimulating hormone (FSH) levels in females of non-child bearing potential will be evaluated at the Screening Visit.

7.5.8 Urine Pregnancy Testing

All female subjects will have urine pregnancy testing at the Screening Visit, at Admission, and at the Day of Discharge (Day 5) or early termination. Female subjects with a positive pregnancy test at the Screening Visit or on Day -2 cannot be enrolled and are considered a screening failure. Pregnancy in such subjects will not be followed up as no exposure to the P4M3 IP will have occurred. In any case of a positive pregnancy test, the Investigator will inform the subject about the risks associated with nicotine/tobacco use during pregnancy.

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

7.6 Sample Handling, Storage, and Shipment

All blood samples will be tested for nicotine concentrations at a central laboratory and the safety laboratory samples which will be tested at a local laboratory (see Appendix 2). The safety laboratory

tests, urine drug screen, breath alcohol screen, urine pregnancy tests and urine cotinine tests will be done by the site personnel at the site.

Blood samples

Blood samples will be drawn by qualified and trained site personnel. Subjects should be in a seated position during blood collection. The maximal expected total volume of blood drawn for each subject will be approximately 434 mL. The required aliquots and volumes for assessments of blood/plasma parameters and tests are summarized below.

Samples for determination of nicotine concentrations will be drawn from subjects following a 5 minute rest. The tourniquet should not be applied for more than 1 minute. Blood will be drawn into 4 mL EDTA-2K tubes (lavender top) and the samples will be mixed by gently inverting the tube 8 times. Within 60 minutes of collection, blood samples will be centrifuged at approximately 1000 to 1300 RCF at 5 °C for 10 minutes. Plasma (2 x 1 mL) will be transferred (using methanol rinsed plastic pipettes) into 2 appropriately labelled 3.5 mL methanol rinsed polypropylene screw top tubes. Samples will be transferred to a freezer (-20 °C) within 120 minutes of collection. Samples will be shipped on dry ice to the bioanalytical facility, a shipment inventory in excel format will also be sent containing the following information:

- Numeric accession – sample barcode
- Patient Number – subject number including the site identifier
- Analyte – Nicotine, CYP2A6
- Visit Description – (e.g., V1, V2)
- Day Nominal – Day of collection
- Minute Nominal – 0 minute
- Sample type – For analysis or Back-up
- Protocol – P4M3-PK-02
- Collection Date – Date of collection (DD-MMM-YYYY)
- Spec Type - (e.g. frozen)

The clinical staff must be non-smokers and should avoid contact to smoke at least 24 hours before handling blood samples to avoid contamination of the samples with nicotine.

Safety laboratory samples will be destroyed as by the laboratories standard procedures. All other samples will be destroyed after the bioanalytical report has been finalized or the database has been locked, whichever comes last. The facility/-ies at which the samples are stored will be informed in writing by the Sponsor when destruction of the samples shall be performed.

7.7 Questionnaires

The subject questionnaires as appropriate will be entered by the subject directly following both fixed and *ad libitum* use. The questionnaires will be reviewed for completeness by the study site collaborator and subjects will be requested to complete any missing information.

Symptoms or worsening of symptoms as documented on any of the questionnaires or the VAS do not need to be documented as AEs because the questionnaire and the VAS will be analysed as part of the report. However, it is at the discretion of the Investigator to document such symptoms also as AEs. The main source for AE collection will be the face-to-face interview between the subject and site staff using, open, non-directive questions (see section Section 8.2.1).

7.7.1 Adapted Version of the Modified Cigarette Evaluation Questionnaire

An adapted mCEQ (Rose *et al* 1998) will be completed by each subject within 60 minutes after product use on Days 1 to 4 after each *ad libitum* session. The questionnaire will be reviewed for completeness by the study site study collaborator and subjects will be requested to complete any missing information.

The questionnaire to be used adapts the wording of mCEQ items to RRPs, following a similar approach of Hatsukami (Hatsukami *et al*, 2013) with the Product Evaluation Scale (PES) which is an adaptation of the mCEQ for oral tobacco products.

7.7.2 Sensory Questionnaire

A sensory questionnaire adapted from Rose *et al* 2010 will be completed by each subject within 60 minutes after product use on Days 1 to 4 after each *ad libitum* session. The questionnaires will be reviewed for completeness by the study site study collaborator and subjects will be requested to complete any missing information. The SQ assesses the subject's opinion on the following sensory parameters:

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

7.7.3 Visual Analogue Scale for Craving

The VAS craving will be completed by the subject himself/herself. The first assessment will be done prior to T0 of each fixed puffing regimen and *ad libitum* use on Days -1 to 4. All other assessments will be done after T0, at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours on each of Day -1 to Day 4.

The questionnaire will be reviewed for completeness by the study site study collaborator and subjects will be requested to complete any missing information.

7.7.4 Cough Assessment

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

will be asked to complete a cough assessment questionnaire (which includes a VAS, three Likert scales, and an open question).

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

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

- The intensity of cough will be assessed on a 5-point Likert scale ranging from 1 to 5:

  1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe.

- The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5:

  1 = rarely; 2 = sometimes; 3 = fairly often; 4 = often; 5 = almost always.

- The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3:

  0 = no sputum; 1 = a moderate amount of sputum; 2 = a larger amount of sputum;

  3 = a very large amount of sputum.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

An 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 IPs.

8.1.2 Serious Adverse Events

A 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, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate 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)

Clinical conditions that existed before the start of the period of collection (concomitant disease), and whose severity remained unchanged after that point, should not be considered AEs and should not be captured as such. This includes medical therapies or surgical interventions that had been planned before the start of the period of collection regardless of involving admissions to hospital, if the medical condition to be addressed did not get worse after that point. Otherwise, any medical condition that existed before the start of the period of collection and whose severity or frequency increased after that point is to be captured as an AE or SAE, depending on the seriousness criteria met.

8.2 Assessment of Adverse Events

8.2.1 Collection of Information

Any non-serious AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's 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 page of the CRF, and on the SAE form.

AEs should be collected mainly via face-to-face interview with the subject through spontaneous reporting or by the use of consistent, open, non-directive questions from the investigational site collaborators (e.g., "Have you had any health problems since you were last asked? or "How have you been feeling since you were last asked?").

Information recorded will include: verbatim description of the AE/SAE, start and stop dates, seriousness, severity (intensity), action taken (e.g., whether or not the AE/SAE led to the subject's discontinuation from the study), and outcome (e.g., resolved).

Information to be recorded about an SAE should also include, whenever possible, onset and resolution dates and times, circumstances leading up to the event, clinical elements such as clinical course, specific vital signs and test results that may explain the pathophysiology of the event, as well as alternative explanations to its occurrence.

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. Otherwise, each one of those signs and/or symptoms should be reported separately as event terms.

8.2.2 Period of Collection

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

AEs (including SAEs) will be collected from the time of ICF signature until the end of the study (EOS). AEs (including SAEs) will be collected from the time of ICF signature until the EOS.

During a 7-day passive safety FU, there will be recording of spontaneously reported new AEs/SAEs and the active follow-up of ongoing AEs/SAEs by the study site. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found and until the end of the study.

Any AEs or SAEs that are ongoing at the end of the passive safety FU will be managed as described in Section 8.2.6.

SAEs spontaneously reported to the PI after the end of the passive safety FU and considered related to the IP must also be reported to the Sponsor.

8.2.3 Intensity of Adverse Event

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

Mild: Easily tolerated, not interfering with normal everyday activities.

Moderate: Interferes with normal daily activity, but the subject is still able to function.

Severe: Incapacitating and requires 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 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 administration 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 IPs will be assessed for its expectedness. An AE will be regarded as "unexpected" if its nature or severity is not consistent with the information already recorded about the IP P4M3 in Section 6.5 of the current IB.

Table 3 presents expected AEs for the subjects' own e-cigarettes.

Table 3. Expected AEs: Foreseeable Risks with Subjects' Own e-Cigarette Use

Risks Associated with:	Potential Adverse Events
Over-exposure to nicotine / nicotine acute intoxication / poisoning	Mild intoxication: Nausea, hyper-salivation, abdominal pain, vomiting, diarrhea, cold sweat, diaphoresis, headache, dizziness, hearing and visual disturbances, mental confusion, agitation, tremor, weakness, weak analgesia, increase of respiratory reflex and coughing, increase bronchial secretions, shortness of breath (as a consequence of stimulation of lung mechanoreceptors), increase in heart rate and blood pressure
Under-exposure to nicotine / tobacco and nicotine withdrawal symptoms	Affective symptoms: Irritability/anger/frustration, anxiety/anxious/nervous, depressed mood /depression/ sad/ anhedonia, insomnia/sleep problems, dysphoria, hyperalgesia, impatient, restlessness, nightmares/ dreaming Somatic symptoms: tremors, bradycardia, gastrointestinal discomfort, nausea, constipation, increased appetite, hungry, weight gain, coughing, dizziness, sore throat, mouth ulcer Cognitive symptoms: difficulty concentrating, impaired memory
Hypersensitivity reactions	Susceptible consumers may experience hypersensitivity reactions such as skin disorders (e.g., localized or generalized rash, pruritus), urticaria and/or angioedema

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

Any non-serious AE that is ongoing during the passive safety FU will be actively followed-up by the Investigator during that 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).

At the end of the passive safety FU, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for them anymore by the Investigator. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly.

All SAE will be followed up by the Investigator, despite their continuation after the end of the passive safety FU, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

8.3 Reporting and Follow-Up of Serious Adverse Events

Any SAE observed during the period of collection by any of the parties involved in this study (including the Investigational site personnel) must be reported by that party within 24 hours of first awareness to UBC Pharmacovigilance, as described in the safety management plan (SMP).

SAEs considered related to the IP and observed by, or reported to, any of the parties involved in this study (including the Investigational site personnel) after the period of collection must also be reported by that party within 24 hours of first awareness to UBC Pharmacovigilance for safety surveillance purposes.

All the SAE report forms must be either faxed or sent as an attachment to an e-mail message to UBC Pharmacovigilance:

UBC Pharmacovigilance:	Fax number:	[redacted]
	E-mail:	[redacted]
	Address:	United BioSource Corporation UBC Pharmacovigilance 16, Chemin des Coquelicots 1214 Vernier/Geneva Switzerland

As further information regarding an already reported SAE becomes known to any of the parties involved in this study, such follow-up information must be reported on a new SAE report form, marked as a follow-up report and submitted to UBC Pharmacovigilance according to the same timelines described above. The follow-up SAE report form must include the minimum information required for completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form generally supersedes any information that was initially reported.

The SAE report form to be used in this study is provided as a separate document. All SAEs will also be recorded on the relevant CRF page, in addition to the SAE report form.

The Investigator or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the local IRB), according to local regulations and in line with the respective safety management plan.

If applicable, SAEs will be reported by Sponsor to the Center for Tobacco Products Office of Science within 15 days after the report is received by the Sponsor.

8.4 Reporting of Other Events Critical to Safety Evaluations

8.4.1 Abnormal Results of Laboratory Tests

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the Investigator and assessed for clinical significance according to its severity. The severity of abnormal laboratory test result must be assessed using CTCAE version 4.0 grading scale, available in Appendix 3. Whenever that grading scheme is not available for the laboratory result of concern, the Investigator should assess the severity and the clinical significance of that result using his/her medical judgment.

Abnormal laboratory test results detected at the Screening Visit whose CTCAE grades are 2 or higher or still are CTCAE grade 1 and deemed clinically significant are usually concomitant disease or a manifestation of one and must be recorded accordingly. However, in some instances, they may be assessed as AEs (and therefore must be handled according to the directions from Section 8.2 or as manifestations of already reported AEs). This decision will require a careful assessment of the abnormal result within the clinical context on a case-by-case basis and will depend on the Investigator's medical judgment.

Abnormal laboratory test results detected after the Screening Visit whose CTCAE grades are 2 or higher or still are CTCAE grade 1 and deemed clinically significant must be either recorded as AEs (and handled according to the directions in Section 8.2) or linked to a concomitant disease or still to an already reported AE.

The principles for assessing and reporting abnormal laboratory test results, emerging after the Screening Visit, using the CTCAE version 4.0 grading scale, are set up in Table 4:

Table 4. Principles for Assessing and Reporting Abnormal Laboratory Test Results

Grading	Clinically significant?	Is it a worsening from previous results in study?§	Report?
Grade 1	No	Not applicable	No
Grade 1	Yes	No	No*
Grade 1	Yes	Yes	Yes, as AE or linked to an already reported AE
Grade 2 or higher	No/Yes	No	No*
Grade 2 or higher	No/Yes	Yes	Yes, as AE or linked to an already reported AE

* In this situation, this abnormal lab test result is either a manifestation of a concomitant disease or of an already reported AE.
§ Grade increase in this context means the value is higher than the one from the screening visit.

Any other abnormal clinical laboratory result (including those that are not part of the core safety assessments) can, at the discretion of the Investigator, be reviewed and assessed. Even if they do not meet the criteria of the CTCAE grading scheme, the Investigator may consider them to be of clinical significance and, if they are, must report them as AEs.

In general, laboratory values will be recorded as "increased <lab parameter>" or "decreased <lab parameter>" to ensure consistency of recording/coding.

8.4.2 Reporting Other Abnormal Findings

Other abnormal findings discovered during different clinical assessments (e.g., ECG, spirometry, physical examination, vital signs, body weight) should be evaluated for the clinical significance by the Investigator/designee based on his/her medical judgement. All abnormal clinical significant test results or clinical examination findings can, at the discretion of the Investigator, to 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 first exposure to the IP will be will be considered a reason for screen failure. No pregnancy form will be filled in that case, however the diagnosed pregnancy must be captured in the screen failure page of the CRF.

Any pregnancy that was potentially associated with exposure to the IP, including pregnancies spontaneously reported to the Investigator after the EOS must be reported by the Investigator and followed-up until the pregnancy outcome is reached (e.g., normal delivery, spontaneous abortion, voluntary termination) and also until 8 weeks after delivery. Potential association with the exposure to the IP is defined as exposure to IP during or after the calculated conception date.

Any pregnancy complication, adverse pregnancy outcome or maternal complications will be recorded as an AE accordingly.

8.5.2 Reporting of Pregnancies

A dedicated pregnancy form will be used to report reportable cases of pregnancy.

The procedure to report a pregnancy and provide any additional/follow-up information to UBC Pharmacovigilance is the same manner and performed within the same timelines as the one described for an SAE (Section 8.3).

The Investigator is responsible for informing the corresponding IRB of any pregnancy case that was reported during the study, as determined by local regulations. The Investigator is also responsible for providing UBC Pharmacovigilance immediately with the acknowledgement of submission of pregnancy cases issued by the corresponding IRB.

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 the day of discontinuation and will enter the period of passive safety FU. The Investigator will follow-up these AEs until they have been resolved, stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found for them. In general, all AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation has been found and until the end of the study. Any AEs or SAEs that are ongoing at the end of the passive safety FU will be managed as described in Section 8.2.6.

8.7 Investigational Device Misuse

Any occurrences of the P4M3 misuse (use not in accordance with its label and/or instruction) by a subject will be documented by the Investigator or his/her designated staff using a Device Issue Log. Information regarding device misuse should be actively collected during the study visits.

Investigational device misuse may result in use-related hazards.

Use-related hazards are derived from the US Food and Drug Administration Medical Device Use-Safety Guidance (FDA, 2012b):

- Hazards caused specifically by how a device is used
- Unanticipated use scenarios (e.g., modification of Charger, applying any chemicals, using conventional cigarettes, mechanical damage of the device, etc.) that result in hazards must be documented and reported by the Investigator or designee".

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

The process of capturing, assessing, and reporting AEs is described in details in the Safety Management Plan.

8.8 Investigational Device Malfunction

Any occurrences of malfunction of the P4M3 will be documented by the Investigator or his/her designated staff using a Device Issue Log. Information regarding device malfunction should be actively collected during the study visits.

Furthermore, any malfunctions of the P4M3 that lead to an AE/SAE will follow the same processes as described above.

9 STUDY ACTIVITIES

A detailed schedule of assessments can be found in Appendix 1. The investigational site may adjust the start times of scheduled events as long as the necessary relative timing of the previous and subsequent events are maintained. Measurements not conducted at the exact time point, but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the scheduled time point.

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

9.1 Screening Visit

The Screening Visit will be performed within 3 weeks (Day -23 to Day -3) prior to Admission (Day -2).

The following assessments will be performed at the Screening Visit (Table 5) (the sequence of the assessment will be at the discretion of the site but all of them must be done after signature of the ICF).

Table 5. Event Schedule – Screening

Blood sample	Procedures	Additional information
	Informed consent	
	Debriefing/demonstration on IP	
	Demographic data	
	Prior/concomitant medication	
	Medical history/concomitant diseases	
	Vital signs (pulse rate, systolic and diastolic blood pressure, respiratory rate)	At least 5 minutes in supine position prior to measurement
	Height, weight, including calculated BMI	
√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	
√	Serology for HIV and hepatitis B and C	
	Smoking history and e-cigarette use including current brand information	
	Urine drug screen	
	Breath alcohol screen	
	CO breath test	
	Urine pregnancy test for female subjects	
√	Serum FSH for female subjects of non-child bearing potential	
	P4M3 product demonstration	
	Spirometry with and without short-acting bronchodilator	
	ECG	At least 10 minutes in supine position prior to recording
	AE/SAE questioning	If the Screening Visit is performed on two separate days the AE/SAE questions will be asked again
	Physical examination	
	Urine cotinine screening test	
	Inclusion/exclusion criteria	

Abbreviations: AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; FSH = Follicle-stimulating hormone; HIV = Human immunodeficiency virus; SAE = Serious adverse event

9.2 Admission Day -2

The following assessments will be performed at admission (Day -2) (Table 6):

Table 6. Event Schedule – Day -2 Admission

Blood sample	Procedures	Additional information
	Recheck of selected inclusion/exclusion criteria	
	Urine pregnancy test for female subjects	Pregnancy test results are to be available prior to P4M3 product test
√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	Fasting state
	Urine cotinine screening test	
	Urine drug screen	
	Breath alcohol screen	
	CO breath test	
	Vital signs	At least 5 minutes in supine position prior to measurement
	Physical examination	
	Breakfast	
	Debriefing on P4M3	
	Enrollment	
√	*Trans*-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma	To be performed post enrollment and prior to product test
	P4M3 product test with HPT	Product test with P4M3-1.7% *ad libitum* for a maximum of 10 minutes.
	Assessment of cough (VAS, three Likert scales and one open question)	Completed by the subject on site within 30 minutes of product use
	Vital signs	At least 5 minutes in supine position prior to measurement, to be conducted at 60 minutes ± 10 minutes post end of product use
	Evening meal	
	Snack	
	Support during periods of abstinence from nicotine usage as required	All day as required
	AE/SAE recording, concomitant medication	All day

Abbreviations: AE = Adverse event; BMI = Body mass index; CYP2A6 = Cytochrome P450 2A6; SAE = Serious adverse event

9.3 Baseline and Investigational Period

9.3.1 Day -1 (Baseline) to Days 1 to 4 of Investigational Product Use

On the days of fixed puffing (morning) and *ad libitum* use (afternoon) with HPT, assessments will be performed as detailed in Table 7 and Table 8.

Table 7. Event Schedule – Fixed Puffing and *Ad Libitum* Product Use With Subjects' Own e-Cigarette (Days -1)

Blood sample	Procedures	Additional information
	Optional morning snack	
√	Nicotine baseline plasma sampling prior subjects' own e-cigarette use	One blood sample will be taken prior to the start of product use (T0): 15 minutes ± 5 minutes (T-1).
	Vital signs prior product use (x1 T0)	At least 5 minutes in supine position prior to measurement
	VAS for craving prior product use (x1 T0)	
	Washout	Minimum of 10 hours
	Fixed puffing subjects' own e-cigarette with HPT	Fixed puffing regimen comprising of 12 puffs in total at a rate of one puff every 30 seconds (± 5 seconds)
√	Plasma samples for nicotine	Post T0, blood will be drawn at the following time points: T1 after 2 minutes ± 30 seconds, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, T9 after 4 hours ± 5 minutes.

	VAS Craving assessment	Post T0, VAS assessments will be assessed at the following time points 4 minutes (± 2 minutes) 10 minutes (± 2 minutes) 15 minutes (± 2 minutes) 30 minutes (± 5 minutes) 1 hour (± 10 minutes) 2 hours (± 10 minutes) 4 hours (± 10 minutes)
	SQ assessment	Within 60 minutes after completion of product use
	Assessment of cough (VAS, three Likert scales and one open question)	Completed by the subject on site within 30 minutes of product use
	Vital signs	At least 5 minutes in supine position prior to measurement, to be conducted at 60 minutes ± 10 minutes post end of product use
	Device events malfunctions/misuse	As reported post product use
	Lunch	
	Vital signs pre-product use	At least 5 minutes in supine position prior to measurement
	VAS for craving pre-product use (x1 T0)	
√	Nicotine baseline plasma sampling (x1 T0) prior subject's own e-cigarette use	One blood sample will be taken prior to *ad libitum* product use (T0): 15 minutes ± 5 minutes (T-1)
	Washout	Minimum of 10 hours
	Ad libitum use subject's own e-cigarette with HPT	*Ad libitum* use for 60 minutes (± 5 minutes) with HPT recording
√	Plasma samples for nicotine	Post T0, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes, T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, T7 after 4 hours ± 5 minutes.

VAS Craving assessment	Post T0, VAS assessments will be assessed at the following time points 10 minutes (± 2 minutes) 20 minutes (± 2 minutes) 30 minutes (± 5 minutes) 40 minutes (± 5 minutes) 1 hour (± 10 minutes) 2 hours (± 10 minutes) 4 hours (± 10 minutes)
Assessment of cough (VAS, three Likert scales and one open question)	Completed by the subject on site within 30 minutes of product use
Adapted mCEQ assessment	Within 60 minutes after completion of product use
SQ assessment	Within 60 minutes after completion of product use
Vital signs	At least 5 minutes in supine position prior to measurement, to be conducted at 60 minutes ± 10 minutes post end of product use
Device events malfunctions/misuse	As reported post product use
Evening meal	
Snack	
Support during nicotine abstinence as required	All day as required
AE/SAE recording, concomitant medication	All day

Abbreviations: AE = Adverse event; SAE = Serious adverse event, VAS = Visual analogue scale, Adapted mCEQ = Adapted version of the modified Cigarette Evaluation Questionnaire, SQ = Sensory questionnaire

Table 8. Event Schedule – Fixed Puffing and *Ad Libitum* Product Use with P4M3 Variants (Days 1 to 4)

Blood sample	Procedures	Additional information
	Optional morning snack	
	Randomization **(Day 1 only)**	Sequence 1: P4M3-1.7%; P4M3-1.7%LA; P4M3-3%LA; and P4M3-4%LA Sequence 2: P4M3-1.7%LA; P4M3-1.7%; P4M3-3%LA; and P4M3-4%LA
√	Nicotine baseline plasma sampling prior P4M3 variants use	One blood sample will be taken prior to the start of product use (T0): 15 minutes ± 5 minutes (T-1).
√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry) **(Day 2 only)**	Fasting state
	Vital signs prior product use	At least 5 minutes in supine position prior to measurement
	VAS for craving prior product use (x1 T0)	
	Washout	Minimum of 10 hours
	Fixed puffing P4M3 variants with HPT	Fixed puffing regimen comprising of 12 puffs in total at a rate of one puff every 30 seconds (± 5 seconds)
√	Plasma samples for nicotine	Post T0, blood will be drawn at the following time points: T1 after 2 minutes ± 30 seconds, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, T9 after 4 hours ± 5 minutes.

	VAS Craving assessment	Post T0, VAS assessments will be assessed at the following time points 4 minutes (± 2 minutes) 10 minutes (± 2 minutes) 15 minutes (± 2 minutes) 30 minutes (± 5 minutes) 1 hour (± 10 minutes) 2 hours (± 10 minutes) 4 hours (± 10 minutes)
	SQ assessment	Within 60 minutes after completion of product use
	Assessment of cough (VAS, three Likert scales and one open question)	Completed by the subject on site within 30 minutes of product use
	Vital signs	At least 5 minutes in supine position prior to measurement, to be conducted at 60 minutes ± 10 minutes post end of product use
	Device events malfunctions/misuse	As reported post product use
	Washout	Minimum 10 hours
	Lunch	
	Vital signs pre-product use	At least 5 minutes in supine position prior to measurement
	VAS for craving prior product use (x1 T0)	
√	Nicotine baseline plasma sampling (x1 T0) prior P4M3 variants *ad libitum* use	One blood sample will be taken prior to P4M3 variants *ad libitum* use (T0): 15 minutes ± 5 minutes (T-1)
	Ad libitum use P4M3 variants with HPT	*Ad libitum* use for 60 minutes (± 5 minutes) with HPT recording
√	Plasma samples for nicotine	Post T0, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes, T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, T7 after 4 hours ± 5 minutes.

VAS Craving assessment	Post T0, VAS assessments will be assessed at the following time points: 10 minutes (± 2 minutes) 20 minutes (± 2 minutes) 30 minutes (± 5 minutes) 40 minutes (± 5 minutes) 1 hour (± 10 minutes) 2 hours (± 10 minutes) 4 hours (± 10 minutes)
Assessment of cough (VAS, three Likert scales and one open question)	Completed by the subject on site within 30 minutes of product use
Adapted mCEQ assessment	Within 60 minutes after completion of product use
SQ assessment	Within 60 minutes after completion of product use
Vital signs	At least 5 minutes in supine position prior to measurement, to be conducted at 60 minutes ± 10 minutes post end of product use
Device events malfunctions/misuse	As reported post product use
Evening Meal	
Snack	
Support during nicotine abstinence as required	All day as required
AE/SAE recording, concomitant medication	All day

Abbreviations: AE = Adverse event; SAE = Serious adverse event, VAS = Visual analogue scale, Adapted mCEQ = Adapted version of the modified Cigarette Evaluation Questionnaire, SQ = Sensory questionnaire

9.4 Day of Discharge

The following assessments will be conducted prior to the time of Discharge on Day 5 (Table 9):

Table 9. Event Schedule – Day 5 Discharge

Blood sample	Procedures	Additional information
	Optional morning snack	
	AE/SAE recording, concomitant medication	All day
	Assessment of cough (VAS, three Likert scales and one open question)	
√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	This laboratory assessment will be performed on the morning of Day 5 under fasting conditions
	Washout	Needs to be maintained
√	Plasma samples for determination of subject's nicotine $t_{1/2z}$	Post T0 (start of the last product use), blood will be drawn at the following time points: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes, T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes, T5 after 24 hours ± 30 minutes.
	Urine pregnancy test for female subjects	
	Vital signs	At least 5 minutes in supine position prior to measurement
	ECG	At least 10 minutes in supine position prior to recording
	Spirometry without short-acting bronchodilator	
	Physical examination	
	Support during nicotine abstinence as required	All day as required
	Debriefing on IP	
	Time of discharge	

Abbreviations: AE = Adverse event; ECG = Electrocardiogram, SAE = Serious adverse event, VAS = Visual analogue scale, Adapted mCEQ = Adapted version of the modified Cigarette Evaluation Questionnaire, SQ = Sensory questionnaire

9.5 Early Termination Procedures

The following assessments will be conducted after a subject is prematurely discontinued from the study (Table 10):

Table 10. Event Schedule – Early Termination

Blood sample	Procedures	Additional information
	AE/SAE recording, concomitant medication	
	Assessment of cough (VAS, three Likert scales and one open question)	
√	Clinical laboratory parameters (hematology, urine analysis, clinical chemistry)	
	Urine pregnancy test for female subjects	
	Vital signs	At least 5 minutes in supine position prior to measurement
	ECG	At least 10 minutes in supine position prior to recording
	Spirometry without short-acting bronchodilator	
	Physical examination	
	Time of early termination	

Abbreviations: AE = Adverse event; ECG = Electrocardiogram, SAE = Serious adverse event

9.6 Passive Safety Follow-up Period

After the time of Discharge at Day 5 (or if prematurely discontinued from the study), subjects will enter a 7-day passive safety FU during which there will be recording of spontaneously reported new AE/SAEs and the active follow-up of ongoing AE/SAEs by the study site.

Any AEs or SAEs that are ongoing at the end of the 7-day passive safety FU will be handled as described in Section 8.2.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

An independent Clinical Research Associate ("Monitor") not involved with the study site will be responsible for the monitoring of the study. Monitoring will be performed according to the study CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

The Investigator shall permit the Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the Monitor so that entries in the CRFs may be verified. The Investigator, as part of their responsibilities, is expected to ensure that the study adheres to GCP requirements.

The site initiation visit will be conducted by the Monitor and, if necessary, with the Sponsor or its authorized representative. The purpose of the site initiation visit is detailed in the monitoring plan. The general training of the study procedures and specific training on selected procedures will be performed and documented.

Communication by telephone, mail, and e-mail may be used as needed to supplement site visits. The 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 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 Investigator, or a designated member of the Investigator's staff, must be available during the monitoring visit to review the data and resolve any queries, and to allow direct access to the subject's records for source data verification.

10.2 Training of Staff

During the site initiation visit, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training in the relevant systems and other study-specific procedures. The activities of the site initiation visit will be described in the monitoring plan.

The Investigator 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 to the staff involved in a timely manner. The Investigator will maintain a record of all individuals involved in the study.

10.3 Audits and Inspections

GCP 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 IRB 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, and any applicable regulatory requirements. The Investigator will contact the Sponsor or the authorized representative immediately, if contacted by a regulatory agency about an inspection at their site.

The Investigator and study staff 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 Investigator understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All Data Management Activities will be described in detail in the Data Management Plan and documents specified therein.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

With the exception of the subject-reported outcome data, all results from the clinical assessments will be recorded in the Source Documents by the Investigator or their authorized designee(s) and then captured in the CRFs at the study site. The subject questionnaires and the VAS will be entered by the subject directly. 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 then transferring the data into the CRF, in accordance with the Case Report Form 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 corrections 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 study site by the Clinical Research Associate. 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 informed consent form.

11.1.2 Protocol Deviations

Protocol deviations are defined as those deviations from any procedure as defined in this document, including but not limited to, as any violation of inclusion/exclusion criteria, use of any nicotine or tobacco-containing product other than the assigned product during each of the exposure period, use of any nicotine tobacco-containing product during wash-out periods, assessments not performed or performed outside the scheduled time windows, or use of estrogen or other drugs that are known to affect CYP2A6 activity.

All protocol deviations will be documented appropriately in an approved format.

Information from the source documents will represent the primary source of protocol deviations. Information following site monitoring and other manual reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and will be recorded and tracked in an 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 following site monitoring and other manual reviews, will be reviewed against the individual data points in the CRF database but will not be formally reconciled with the CRF database (e.g., their description or occurrence date). The overall procedure for managing protocol deviations are described in the SOPs of the CRO Data Management Team. All deviations will be reviewed periodically, as determined 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 Data Management Team at the CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the CRO Data Management Team. The Data Management Team at the CRO will prepare a Data Management Plan, to be reviewed and approved by the Sponsor, prior to the start of the study. This document will describe, in detail, the procedures and processes related to Data Management.

All data of all subjects successfully enrolled, as well as subjects who failed screening, and/or experienced an AE during the study (from time of signing the informed consent form to the end of the passive safety FU), will be captured and stored in the study database.

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

11.2.1 Data Validation

The data will be validated as defined in the Data Management Plan and Data Validation Specifications. Discrepancy lists will be generated electronically, as necessary.

Data queries will be raised 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, medical/surgical history, and 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:	MedDRA®
Medications:	WHO Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical classification system

11.2.3 Database Lock

When all outstanding Data Management issues have been resolved and all validation, quality review and cleaning activities are complete, the database or selected data is/are declared soft-locked. Access to change data in the soft-locked database or to change selected data at this time is limited.

After data review by the Sponsor, resolution of all raised queries and quality control of the changed data, the database or selected data thereof will be declared locked upon Sponsor approval, as applicable.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the Data Management and Statistical Team at the CRO. Any of those changes must be documented in the database log file.

After study completion, the study database will be transferred to the Sponsor in the format specified in the Data Management Plan in the Clinical Data Interchange Standards Consortium Study Data Tabulation Model Data Structure Specifications.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Full details of the statistical analysis will be given in a statistical analysis plan (SAP). Any changes to the planned statistical methods will be documented in the Clinical Study Report. The statistical evaluation will be performed using SAS®, Version 9.3 or later.

12.1.1 Definitions for Statistical Data Analysis

Unless otherwise stated, for the purposes of statistical analyses, baseline is defined as the last available time point prior to T0 on Day -1.

Nicotine exposure parameters will be derived from plasma nicotine versus time data by NCA using Phoenix WinNonlin, Version 7.0 or higher. Cmax, AUCs, and related PK parameters, as appropriate, will also be calculated. To minimize the potential bias in the nicotine plasma PK parameters for the fixed puffing regimens, background-concentration correction will be applied to the concentration data and derived PK parameters to adjust for carry-over effects. For nicotine exposure parameters, baseline (C_0) will be defined as the concentration immediately prior to T0 for each session. The baseline correction will be implemented by calculating the nicotine exposure parameters using adjusted concentration values as described below:

The nicotine terminal elimination rate constant λ_z (and $t_{1/2z}$) will be estimated from the Day 5 PK samples (or early termination samples, if available) using a linear regression on the log concentration the pre-T0 time points. The regression analysis should contain data from at least 3 different time points in the terminal phase (including the last quantifiable concentration but excluding the concentration at t_{max}), consistent with the assessment of a straight line on the log-transformed scale. The nicotine plasma background-corrected PK parameters will be derived by performing the NCA on the corrected concentrations.

For the purposes of background-correction of the plasma concentrations post-baseline the following formula will be applied: $cC_t = C_t - C_0 * e^{-\lambda zt}$. Where, C_t is the corrected concentration at each time point, C_0 is the pre-use baseline concentration, λ_z is the Day 5 (or early termination, if available) terminal elimination rate constant and t is the actual time.

If plasma concentrations cannot be background-corrected in a sufficient number of subjects e.g., in the event that the λ_z (or $t_{1/2z}$) cannot be estimated, modelling approaches may be applied including conventional compartmental analyses. The total (untransformed) PK parameters will be reported and used for statistical analyses instead in case both correction methods are unsuccessful. If warranted, nonlinear mixed-effect modeling using nicotine pooled data across studies may also be used.

Additional nicotine PK parameters may be determined and reported in order to support the interpretation where appropriate.

A more detailed description of the analyses will be presented in the SAP.

12.1.2 Descriptive Statistics

All endpoints will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data, arithmetic means and standard deviations (mean and SD), median, minimum and maximum. For log normally distributed endpoints geometric mean, geometric CV will also be presented (note: categorical variables will be summarized by frequency statistics [number and percentage]). For endpoints relating to sampling times (e.g. t_{max}) only median and range will be presented. All analyses and summaries will be performed separately for fixed puffing and *ad libitum* use, with the exception of AEs.

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

In general, missing data will not be imputed in this study, due to the nature of the measurements and the short periods of exposure and use. However, for questionnaire data total scores and domain or subscale scores may use a certain degree of imputation by averaging across individual item scores. Further details will be provided in the SAP.

In general, for the estimation of PK parameters, values below the lower limit of quantification (LLOQ) will be treated as missing and will be ignored in the PK evaluation.

12.2 Determination of Sample Size and Power Consideration

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

12.3 Analysis Populations

All analyses will be based on actual product exposure. All endpoints (other than safety) will be analyzed using the nicotine PK analysis sets. Safety will be analyzed using the safety population.

12.3.1 Pharmacokinetic Population

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

12.3.2 Pharmacodynamic Population

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

12.3.3 Safety Population

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

12.4 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be reported for the safety population. Appropriate summary statistics will be provided.

12.5 Primary Objectives and Endpoints

12.5.1 Primary Endpoint Analysis Variables

Nicotine exposure parameters for *ad libitum* use will be derived from plasma nicotine concentration versus time data using a non-compartmental technique. In particular:

cC_{peak}	Background-corrected peak plasma nicotine concentration
t_{peak}	Time to peak plasma nicotine concentration during *ad libitum* use, t_{peak} will be reported as long as there is at least one quantifiable concentration post-exposure
cC_{trough}	Background-corrected trough plasma nicotine concentration
$cC_{average}$	Background-corrected average of plasma nicotine concentration between 0 to 1 hour
$cAUCb_{(0\text{-}4h)}$	Background-corrected area under the concentration-time curve that is above the corrected baseline from the start of *ad libitum* use to 4 hours.

Unadjusted PK parameters will also be presented. Additional plasma PK parameters may be derived and/or reported as appropriate.

12.5.2 Statistical Analysis

Endpoints for *ad libitum* use will be summarized as described in Section 12.1.2.

Nicotine PK parameters will be derived from plasma nicotine versus time data using non-compartmental analysis. Plasma PK parameters will be summarized using descriptive statistics by product type (e.g., subjects' own e-cigarette or P4M3 variant), as appropriate.

For the 60-minute *ad libitum* uses, an ANOVA will be conducted on logarithmically transformed cC_{peak}, $cC_{average}$, and $cAUCb_{(0\text{-}4h)}$, as applicable. The model will be adjusted for sex and cC_{trough} value with product use as a fixed effect and subjects as a random effect. Wilcoxon signed-rank test will be used to compare t_{peak} between the test (P4M3 variant) and reference (subject's own) products.

The relationship between nicotine concentrations (with lactic acid only) and the nicotine PK parameters will be investigated graphically on an exploratory basis.

12.6 Secondary Objectives and Endpoints

12.6.1 Secondary Endpoint Analysis Variables

12.6.1.1 Nicotine Exposure Parameters for Fixed Puffing

Nicotine exposure parameters for fixed puffing be derived from plasma nicotine versus time data using a non-compartmental technique. In particular:

cC_{max}	Background-corrected maximum plasma concentration
t_{max}	Time to peak plasma nicotine concentration during fixed puffing product use, t_{peak} will be reported as long as there is at least one quantifiable concentration post-exposure
$cAUC_{(0-4h)}$	Background-corrected area under the concentration-time curve that is above the corrected baseline from the start of fixed puffing product use to 4 hours.

Additional plasma PK parameters may be derived and/or reported as appropriate.

More details on nicotine PK parameter derivations will be provided in the SAP.

12.6.2 Statistical Analysis

Nicotine plasma PK parameters will be determined from the plasma concentration-time profiles for all evaluable subjects according to conventional NCA methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. For the fixed puffing regimen, background-corrected nicotine plasma concentrations will be used for the estimation of plasma PK parameters by NCA. Plasma PK parameters will be summarized using descriptive statistics by study product (i.e., subjects' own e-cigarette or P4M3 variant), as appropriate.

For the fixed puffing regimens, the ratio of geometric mean nicotine exposure normalized $cAUC_{(0-4h)}$ and cC_{max} for each P4M3 variant in reference the subject's own e-cigarette will be presented with associated 90% CIs. The theoretical nicotine exposure, as appropriate, will be used for the purposes of parameter normalization.

In order to evaluate the PK parameters of the P4M3 variants with subjects' own e-cigarette, an ANOVA will be conducted on logarithmically transformed $cAUC_{(0-4h)}$, $cC_{average}$, and cC_{max}, as applicable. The model will include sex and product use as fixed effects and subjects as a random

effect. For each P4M3 variant, the geometric LSM P4M3 variant:e-cigarette ratios will be presented with 90% CIs. The dose-proportionality of the e-liquid concentrations (with lactic acid only) versus nicotine exposure PK parameters will be investigated graphically on an exploratory basis.

In addition, the impact of the lactic acid will be evaluated for the PK parameters, using an ANOVA on logarithmically transformed $cAUC_{(0\text{-}4h)}$ and cC_{max}, adjusting for sex, with sequence, subject nested within sequence, period, and product as fixed effects. The geometric LSM P4M3-1.7%LA:P4M3-1.7% ratios will be presented with 90% CIs. Wilcoxon signed-rank test will be used to compare t_{max} between the study products.

12.6.2.1 VAS Craving Assessments

VAS craving assessments will be summarized by product and product use period. VAS craving assessments that are collected during the product use periods will be summarized over time within each product use period. The scores will be assessed using repeated measures ANCOVA with product use, sex, baseline value, the interaction of product and time point, and time point as fixed effects including the assessment time points as repeated measurements. The interaction term will be removed if $p > 0.1$. Additionally, the VAS craving score will be analyzed as AUC (similar to the calculation of $AUC_{(0\text{-}4h)}$, averaged over the total time) for each product use period and analyzed using the same model as for the nicotine exposure parameters.

12.6.2.2 Questionnaires (Adapted mCEQ and SQ)

Adapted mCEQ subscale scores and SQ answers will be summarized by product and product use period with descriptive statistics and displayed graphically. The scores/answers will be analyzed using an ANOVA adjusted for sex with product use, product, and time point as a fixed effect and subjects as a random effect.

12.6.2.3 Puffing Topography

HPT parameters (Appendix 4) will be summarized by product use period with arithmetic means, %CV, and 90% CIs. In order to evaluate the association between the HPT and the nicotine exposure, HPT parameters will be plotted against the nicotine exposure parameters with product indicated using different symbols for each nicotine concentration.

12.6.3 Safety Endpoints

In general, all safety data will be listed and tabulated using the approach described in Section 12.1.2. Safety variables collected during exposure periods will also be reported by product exposure.

AE data will serve as the primary assessment of safety. Other safety variables monitored in this study include: respiratory symptoms (cough assessment VAS and Likert scales); vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; clinical chemistry, hematology, and urine analysis safety panel; physical examination.

All AEs will be summarized by nicotine concentration (fixed puffing and *ad libitum* use combined) and overall. The number and percentage of subjects with AEs, SAEs, and device events will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to discontinuation, AEs leading to death, AEs by relatedness to product exposure (with and without laboratory related AEs), AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events. Due to the laboratory schedule in this study, any lab related AEs will be assigned to P4M3 4% nicotine concentration.

Summary tables showing actual values and change from baseline of clinical findings will be provided for spirometry, ECGs, vital signs, and laboratory parameter. Descriptive statistics will be summarized by fixed puffing/*ad libitum* use and nicotine concentration and change from baseline will be presented for laboratory parameters, ECG, respiratory symptoms, and vital signs. Shift tables will be provided for laboratory and safety ECG data.

12.7 Exploratory Analyses

There are no planned exploratory analyses.

12.8 Interim Analysis

Quality controlled data of plasma nicotine concentrations will be analyzed. The analysis on the quality controlled data will be performed prior to database lock and the outcome of the analysis will be received and reviewed by the Sponsor. Following this analysis, all data changes and changes to the statistical analysis will be documented in the study report including an assessment of the impact of the change and the status of the data at the time of the change. Alternative modeling approaches will be defined in the statistical analysis plan prior to performing the analysis.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigator and Study Administrative Structure

13.1.1 Investigator

Principal Investigator:	Jonathan Austin, MD High Point Clinical Trials Center 4160 Mendenhall Oaks Pkwy #105 High Point, North Carolina 27265 USA Tel.: +1 [redacted] Fax: +1 [redacted] E-mail: [redacted]

13.1.2 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland Tel: +41 (58) 242 2111 Fax: +41 (58) 242 2811
Steffen Fredersdorf, PhD Study Scientist; Manager Clinical program	Phone: +41 [redacted] E-mail: [redacted]
[redacted], MD Medical Safety Officer	Phone: +41 [redacted] E-mail: [redacted]
[redacted] Study Biostatistician	Phone: +41 [redacted] E-mail: [redacted]

13.1.3 Other Responsibilities

Any SAEs or pregnancies will be handled by:

United BioSource Corporation (UBC) Safety,
16, Chemin des Coquelicots,
1214 Vernier/Geneva,
Switzerland.
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Details of the laboratories conducting the clinical safety laboratory services and bioanalyses are shown in Appendix 3.

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 confidentiality of data for 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 number/code, sex and date of birth, but **not** by name, initial, or any other details relating to an 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 study information sheet and ICF) must be maintained in confidence by the Investigator. 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 Documentation

The Investigator and all study site staff involved with the study must permit direct access to source data/documents for study related monitoring, audits, IRB 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, and scans, X-rays, 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 and any other applicable local or national regulations. For X-rays, at least the radiologist's assessment is required as source documentation. If the actual image is available it can be stored on a CD as well.

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 (ICH GCP E6 (R1), July 1996).

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

- At least 15 years after completion or discontinuation of the study, or
- At least 2 years depending on, for example, the circumstances
- After formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the 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 (if applicable), and Enrollment Log (if applicable).
- Record of all communications between the Investigator and the IRB, composition of the IRB.
- Record of all communications/contact between the Investigator, 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, CVs, and their signatures.
- Investigator Logs.
- CRFs, study specific questionnaires (and associated data/scoring).
- AE reports and details of follow-up investigations, details of concomitant medication.

- All other source documents (e.g., chest X-rays, ECGs, consultation reports, physical examination and 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).
- Record of any body fluids or tissue samples collected and retained.
- 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 Investigator/study site as to when these documents no longer need to be retained.

The Investigator/study site must take measures to prevent accidental or premature destruction of these documents.

If an Investigator wishes to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

The Investigator must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If an Investigator is unable to meet this obligation, they 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 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 IRB will be complied with as requested by local requirements.

13.6 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor. In addition, the Investigators must agree with the Sponsor to commit to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

13.7 Publication and Disclosure Policy

This document contains data, information and trades secretes that are confidential and proprietary to the Sponsor. This document is being provided solely for the purpose of evaluation and/or conducting this clinical study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IRB, 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 clinical 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.

The Sponsor plans to disclose details of the study protocol on a web-based, publicly available, clinical trial register database (e.g., ClinicalTrials.gov).

14 REFERENCE LIST

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Appendix 1 Schedule of Events

Study Day	Day -23 to -3 Screening Visit	Day -2 Admission	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5 Discharge	Passive safety FU
Informed consent	•								
Debriefing on P4M3	•	•							
Inclusion/exclusion criteria	•[1]	•[1]							
P4M3 product test with HPT		•[2]							
Enrollment		•							
Randomization				•					
Fixed puffing own product use with HPT [3]			•						
Ad libitum own product use with HPT [4]			•						
Fixed puffing P4M3 Product use with HPT [3]				•	•	•	•		
Ad libitum P4M3 Product use with HPT [4]				•	•	•	•		
Support during periods of abstinence from nicotine usage (as required)		•	•	•	•	•	•	•	
Identification of current e-cigarette brand and e-liquid nicotine concentration	•								
Smoking history and e-cigarette use	•	•							
Demographics [5], medical history, concomitant diseases	•								
Prior medication [6] / Concomitant medication	•	•	•	•	•	•	•	•	•
Physical examination	•	•						•[14]	
Body height, weight and related BMI	•								
Vital signs	•	•	•[7]	•[7]	•[7]	•[7]	•[7]	•[14]	
ECG	•							•[14]	
Spirometry [8]	•							•[14]	
Carbon monoxide breath test	•	•							
B/U: Hematology, clinical chemistry, urine analysis safety panel	•	•			•			•[14]	
B: Serology	•								

Study Day	Day -23 to -3 Screening Visit	Day -2 Admission	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5 Discharge	Passive safety FU
U: Urine drug screen	•	•							
Breath alcohol screen	•	•							
U: Urine cotinine screen	•	•							
U: Pregnancy test (females)	•	•						• [14]	
B: CYP2A6 activity (trans-3'-hydroxycotinine and cotinine) [9]		•							
B: Plasma nicotine [9]			•	•	•	•	•	•	
VAS craving [10]			•	•	•	•	•		
Adapted mCEQ [11]			•	•	•	•	•		
Sensory Questionnaire [11]			•	•	•	•	•		
Cough assessment [12]		•	•	•	•	•	•	• [14]	
Device Malfunctions/Misuse [13]		•	•	•	•	•	•		
AE/SAE [13]	•	•	•	•	•	•	•	• [14]	•

Abbreviations: AE = Adverse event; B = Blood sample required; BMI = Body mass index; ECG = Electrocardiogram; Adapted mCEQ = Adapted version of the modified Cigarette Evaluation Questionnaire; VAS craving = Visual Analogue Scale for Craving; SAE = Serious adverse event; U = Urine sample required.

1 Selected screening procedures have to be completed, respectively re-verified at Admission prior to enrollment.

2 Subjects will use P4M3 physically connected to the puffing topography device without recording of parameters (HPT device switched off) for one product use experience. After the product test, subjects not willing and/or not ready to use (e.g., intolerance) P4M3 will be discontinued.

3 Subjects will use own e-cigarette (Day -1) and P4M3 (Mornings of Days 1 to 4) with HPT device physically connected in the morning for a fixed puffing of 12 puffs with 30 seconds (± 5 seconds) between each puff over approximately 6 minutes. The used e-liquid cartridges will be collected for assessment of e-liquid use.

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

5 Sex, date of birth/age, and race.

6 All medications taken 4 weeks prior to the Screening Visit will be documented. Prior medication which has an impact on CYP2A6 activity taken within 14 days or within 5 half-lives of the drug (whichever is longer) prior to Admission is an exclusion criteria.

7 Systolic and diastolic blood pressure and pulse and respiratory rate pre- product use and 60 minutes ± 10 minutes post end of product use.

[8] Spirometry with and without bronchodilator at the Screening Visit; without bronchodilator at the time of discharge or as early termination assessments, as applicable.

[9] Blood samples to be taken as follows:

One sample on Day -2 will be taken (post-enrollment and prior to product test) to assess trans-3'-hydroxycotinine and cotinine for determination of CYP2A6 activity of subjects.

On each of Days -1 to 4, a total of 10 blood samples will be taken for fixed puffing PK parameter estimation. One blood sample will be taken prior to the start of product use (T0) 15 minutes ± 5 minutes (T-1). Thereafter in relation to T0, blood will be drawn at the following time points: T1 after 2 minutes ± 30 seconds, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minute, T8 after 2 hours ± 5 minutes, and T9 after 4 hours ± 5 minutes.

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

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

[10] VAS craving: The VAS craving will be completed by the subject himself/herself. The first assessment will be done prior to T0 of each fixed puffing regimen and *ad libitum* use on Days -1 to 4.

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

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

[11] Sensory Questionnaire (SQ; for both fixed puffing and *ad libitum* use) and Adapted mCEQ (for *ad libitum* use only) within 60 minutes after completion of product use by the subjects on Day -1 to Day 4.

[12] Cough assessment: VAS, three Likert scales and one open question. The cough assessment will be completed by the subject on site within 30 minutes after P4M3-1.7% product test at Admission (Day -2) and within 30 minutes after each fixed puffing regimen and *ad libitum* use, and at discharge or at early termination.

[13] Spontaneous reporting of new AEs/SAEs by the subject and active follow-up of ongoing AEs/SAEs by the investigational site including device events and incidence of P4M3 malfunction/misuse.

[14] Assessments should be conducted at the time of discharge or as early termination assessments, as applicable.

Appendix 2 Participating Laboratories

Safety Laboratory

[redacted]
27215 USA
Tel.: +1 [redacted]

Bioanalytical Laboratory

Celerion
[redacted]
68502 USA
Tel.: +1 [redacted]
Fax: +1 [redacted]

Appendix 3 Abnormal Laboratory Values

ABNORMAL LABORATORY VALUES RATING: CLINICAL CHEMISTRY PARAMETERS

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Sodium – Hyponatremia (mmol/L) [0]	<LLN - 130	-	<130 - 120	<120
Sodium – Hypernatremia (mmol/L) [0]	>ULN - 150	>150 - 155	>155 - 160; hospitalization indicated	>160
Potassium – Hyperkalemia (mmol/L) [0]	>ULN - 5.5	>5.5 - 6.0	>6.0 -7.0; hospitalization indicated	>7.0
Potassium – Hypokalemia (mmol/L) [0]	<LLN - 3.0	<LLN - 3.0; symptomatic; intervention indicated	<3.0 - 2.5; hospitalization indicated	<2.5
Glucose – Hypoglycemia [0] (mg/dL) (mmol/L)	 <LLN – 55; <LLN – 3.0	 <55 – 40; <3.0 – 2.2	 <40 – 30; <2.2 – 1.7	 <30; <1.7
Glucose – Hyperglycemia: [0] Fasting (mg/dL) (mmol/L)	 >ULN-160; >ULN-8.9	 >160-250; >8.9-13.9	 >250-500; >13.9-27.8; hospitalization indicated	 >500; >27.8
Creatinine increased [0]	>1 – 1.5 x Baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x Baseline; >1.5 – 3.0 x ULN	>3.0 x Baseline; >3.0 – 6.0 x ULN	>6.0 x ULN
Albumin - Hypoalbuminemia [0] (g/dL) (g/L)	 <LLN – 3; <LLN - 30	 <3 – 2; <30 - 20	 <2; <20	 - -
Alkaline phosphatase increased [0]	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
ALT / AST increased [0]	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Gamma-glutamyl transferase (GGT) increased [0]	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased (total and direct) [0]	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Cholesterol high [0]				
(mg/dL)	>ULN - 300;	>300-400;	>400-500;	>500;
(mmol/L)	>ULN - 7.75	>7.75-10.34	>10.34-12.92	>12.92
Triglycerides - Hypertriglyceridemia [0]				
(mg/dL)	150 – 300;	>300 – 500;	>500 – 1000;	>1000;
(mmol/L)	1.71 – 3.42	>3.42 – 5.70	>5.70 – 11.40	>11.4

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; GGT = Gamma-glutamyl transferase; LLN = Lower limit of the normal range; ULN = Upper limit of the normal range.

Data Sources:

[0] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

ABNORMAL LABORATORY VALUES RATING: HEMATOLOGY PARAMETERS

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Anemia (Hemoglobin) [0] (g/dL) (mmol) (g/L)	 <LLN-10.0 <LLN-6.2 <LLN-100	 < 10-8.0 < 6.2-4.9 < 100-80	 <8.0 <4.9 <80 Transfusion indicated	Life threatening consequences; urgent intervention indicated
Hemoglobin increase [0] – (g/dL)	Increase in >0 – 2 above ULN or above Baseline if Baseline is above ULN	Increase in >2 – 4 above ULN or above Baseline if Baseline is above ULN	Increase in >4 above ULN or above Baseline if Baseline is above ULN	-
WBC Decrease [0] - (cell/mm^3) (10^{-9}/L)	 <LLN – 3000; <LLN – 3.0	 <3000 - 2000; <3.0 – 2.0	 <2000 - 1000; <2.0 – 1.0	 <1000; <1.0
Lymphocytes increase [0] (cell/mm^3)	 -	 >4,000 – 20,000	 >20,000	 -
Lymphocytes decrease [0] (cell/mm^3) (10^{-9}/L)	 <LLN – 800; <LLN – 0.8	 <800 - 500; <0.8 – 0.5	 <500 - 200; <0.5 – 0.2	 <200; <0.2
Neutrophils Decrease [0] (cell/mm^3) (10^{-9}/L)	 <LLN – 1500; <LLN – 1.5	 <1500 - 1000; <1.5 – 1.0	 <1000 - 500; <1.0 – 0.5	 <500; <0.5
Platelets decrease [0] (cell/mm3) (10-9/l)	 <LLN – 75,000; <LLN – 75.0	 <75,000 – 50,000; <75.0 – 50.0	 <50,000 – 25,000; <50.0 – 25.0	 <25,000; <25.0

Abbreviations: LLN = Lower limit of the normal range; ULN = Upper limit of the normal range; WBC = White blood cell.

Data Source:

[0] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

ABNORMAL LABORATORY VALUES RATING: URINE ANALYSIS PARAMETERS

Urine	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Protein[0]	1+ proteinuria; urinary protein <1.0 g/24 hours	2+ proteinuria; urinary protein 1.0-3.4 g/24 hours	Urinary protein ≥3.5 g/24 hours	-

Data Source:

[0] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

Appendix 4 Human Puffing Topography Parameters of P4M3 During Fixed Puffing and *Ad Libitum* Use

Per-Puff Parameters

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

Per-Product Use Parameters

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

Appendix 5 Sponsor Signatures

Study Title: A single-center, open-label, concentration-ranging study to investigate the nicotine pharmacokinetic profiles and pharmacodynamic effects of the P4M3 variants in relation to subjects' own electronic cigarettes in healthy, adult experienced users of electronic cigarettes

Study Number: P4M3-PK-02-US

Final v1.0 10 Jul 2017

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: 13 Jul 2017

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

Signed: [redacted] Date: 13 JUL 2017

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

Signed: [redacted] Date: 13 Jul 2017

[redacted]
Study Biostatistician, Philip Morris Products S.A.

Appendix 6 **Investigator's Signature**

Study Title: A single-center, open–label, concentration-ranging study to investigate the nicotine pharmacokinetic profiles and pharmacodynamic effects of the P4M3 variants in relation to subjects' own electronic cigarettes in healthy, adult experienced users of electronic cigarettes

Study Number: P4M3-PK-02-US

Final v2.0 10 Jul 2017

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

By signing the protocol, the investigator or designee agrees to keep all information and documents provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff. The information provided by the Sponsor to the investigator or designee may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

Signed:_____ Date: 14 Jul 2017

Jonathan Austin, MD
Principal Investigator, High Point Clinical Trials Center