Clinical Study Protocol

P4-PK-04-US

Study title:	A single-center, randomized, controlled, open-label, cross-over study in healthy subjects to investigate the nicotine pharmacokinetic profiles of 2 variants of P4M3 Gen 2.0, an electronic nicotine delivery system, compared to cigarettes
Study number	P4-PK-04-US
Short title	Nicotine pharmacokinetics of P4M3 Gen 2.0 compared to cigarettes
Product name:	P4M3 Gen 2.0
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version:	Final
Date:	14 Oct 2021
Authors:	[redacted], PhD, Clinical Scientist [redacted], PhD, Biostatistician [redacted], MD, Medical Safety Officer

VERSION HISTORY

Version	Date	Protocol Update/Amendment
2.0	14 Oct 2021	Protocol update
Original Document 1.0	28 Sep 2021	Not applicable

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Section	Changes
Synopsis 5.1.2, 7.6.2, 9.1, 9.2 Appendix A	Sars-CoV-2 test removed from study protocol. Sars-CoV-2 test according to local regulation and investigational site requirements.
Synopsis 3.3, 4.1, 6.2.2, 7.8.2; 9.3, 9.4, 9.5, 12.6.2 Appendix A	FR puffing topography device re-named MDEDR puffing topography device

SYNOPSIS

Sponsor:

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

Name of Product:

P4M3 Gen 2.0

Study Title:

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

Study Number:

P4-PK-04-US

Short Study Title:

Nicotine pharmacokinetics of P4M3 Gen 2.0 compared to cigarettes.

Main Objective and Endpoints:

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

   Endpoints (Day 1 to Day 3)

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

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

Secondary Objectives and Endpoints:

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

   Endpoints (Day 1 to Day 3)

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

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

   Related Endpoints (Day 1 to Day 3):

   - Per-puff parameters and per-product use experience parameters from the flight recorder (FR) puffing topography device for 2 variants of P4M3 Gen 2.0 (Appendix D)

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

   Related Endpoint (Day 1 to Day 3)

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

4. To evaluate the safety and tolerability during the study

   Related Endpoints (from Enrollment to EOS):

   - Incidence of adverse events (AEs) and serious adverse events (SAEs)
   - Incidence of P4M3 Gen 2.0 product events including malfunction/misuse
   - Changes in physical examination from baseline
   - Changes in electrocardiogram (ECG) from baseline (heart rate, PR, QRS, QT, QTcF interval)

- Changes in vital signs from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
- Concomitant medication
- Changes in standard spirometry from baseline (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEV_1/FVC)
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel (described in Table 3)

Exploratory Objectives and Endpoints:

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

   Related Endpoints (Day 1 to Day 3)

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

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

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

Study Hypothesis:

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

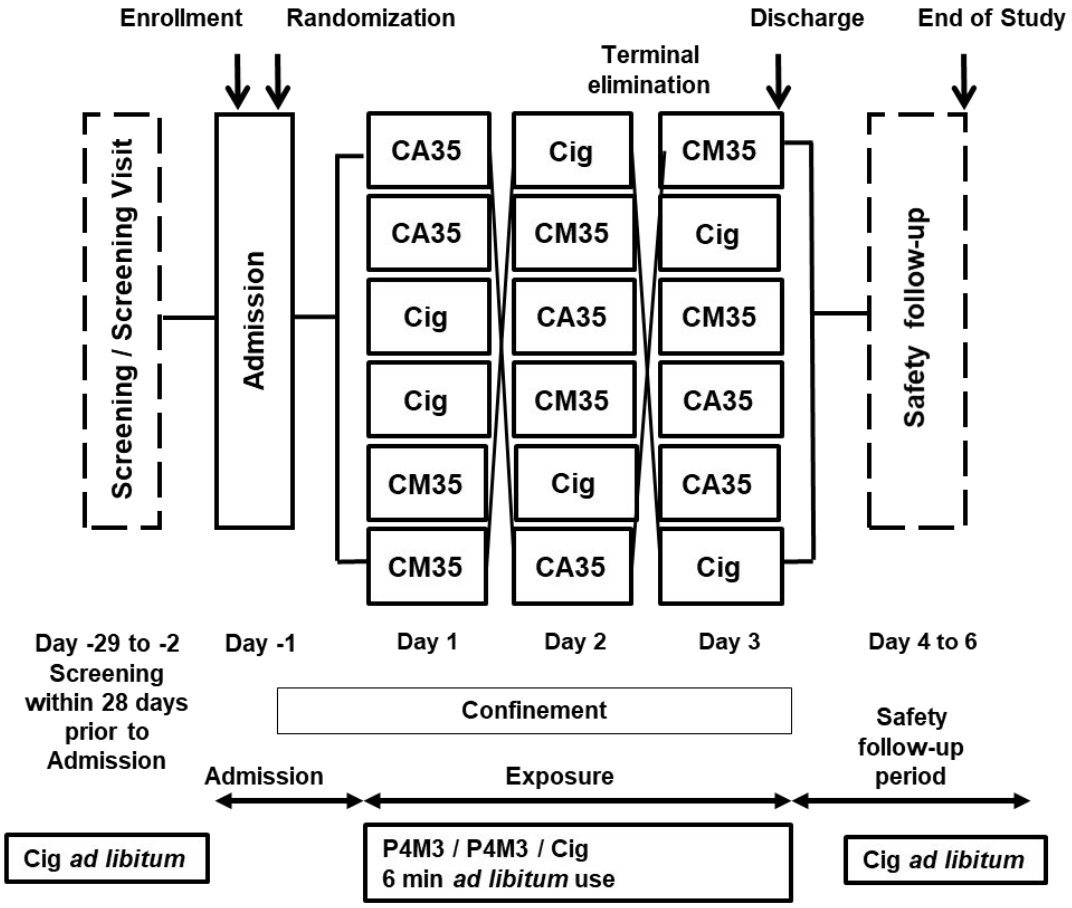
Study Design:

This is a single-center, randomized, controlled, open-label, cross-over study in healthy subjects to investigate the nicotine pharmacokinetic profiles of 2 variants of P4M3 Gen 2.0, an electronic nicotine delivery system (ENDS), compared to cigarettes. In addition, PD

effects (subjective effects and related behavioral assessments) will be evaluated to provide further insights on product evaluation. The study will be conducted with 3 periods and 6 sequences in a cross-over design.

A Screening Visit will be conducted within 28 days (Day -29 to Day -2) prior to Admission (Day -1) to the investigational site (Figure 1). All subjects will undergo a Sars-CoV-2 test according to local regulation and investigational site requirements.

A demonstration of P4M3 Gen 2.0, without product use, will be done by the investigational site staff during the Screening Visit.



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

Figure 1 Study Design

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

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

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

36 subjects will be randomized to 1 of 6 possible sequences of product use on Day 1 to Day 3 (see Figure 1).

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

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

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

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

Prior to T_0:

- T-1: 5 minutes (± 1 minute)

After T_0:

- T1 after 1 minute (+ 30 seconds)
- T2 after 2 minutes (+ 1 minute)
- T3 after 4 minutes (+ 1 minute)

- T4 after 6 minutes (+ 1 minute)
- T5 after 8 minutes (+ 1 minute)
- T6 after 10 minutes (+ 1 minute)
- T7 after 12 minutes (+ 1 minutes)
- T8 after 15 minutes (± 2 minutes)
- T9 after 30 minutes (± 2 minutes)
- T10 after 1 hour (± 5 minutes)
- T11 after 2 hours (± 5 minutes)
- T12 after 4 hours (± 5 minutes)
- T13 after 10 hours (± 5 minutes)
- T14 after 24 hours (± 10 minutes) (Day 1 and Day 2 only)

On Day 2, 14 blood samples will be collected for determination of nicotine PK after allocated product use at the same time points, except timepoint T-1. The sample T14 after T_0 on Day 1 will also be used to determine the nicotine baseline concentration prior to T_0 on Day 2 and similarly, T14 after T_0 on Day 2 for nicotine baseline concentration prior to T_0 on Day 3.

On Day 3, 13 blood samples will be collected for determination of nicotine PK after allocated product use. The sample T14 after T_0 on Day 3 will not be collected.

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

Prior to T_0 (for VAS craving assessment only)

- T-15: within 15 minutes prior to T_0

After T_0: (for VAS craving and VAS liking assessment)

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

- T6 after 2 hours (± 5 minutes)
- T7 after 4 hours (± 5 minutes)
- T8 after 10 hours (± 5 minutes)

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

Additional blood samples will be taken for determination of the nicotine concentration to evaluate terminal elimination half-life ($t_{1/2z}$) in relation to T_0 from Day 2 at the following time points with a time window as indicated in brackets:

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

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

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

Study Population and Main Criteria for Inclusion and Exclusion:

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

1. Subject has signed the ICF and is able to understand the information provided in the ICF.
2. Smoking male or female aged between 24 and 65 years inclusive.
3. Subject has smoked continuously for at least the last 3 years prior to the Screening visit.
4. Subject has smoked ≥ 10 commercially available cigarettes per day for 4 weeks prior to Screening Visit and Admission. Smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).
5. Subject does not plan to quit smoking cigarettes or using other nicotine or tobacco-containing products in the next 3 months.

6. Smoking, healthy subject as judged by the Investigator or designee based on available assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG and medical history).
7. Subject is available for the entire study period and willing to comply with study procedures, including product use assignments and periods of abstinence from any nicotine/tobacco containing products.

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

1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners, or subjects who are involuntarily incarcerated).
3. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease) or any other medical condition (including safety laboratory as per CTCAE), which as per the judgment of the Investigator would jeopardize the safety of the subject.
4. As per the Investigator's judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization), which may interfere with the study participation and/or study results.
5. Subject has donated or received whole blood or blood products within 30 days prior to Screening Visit.
6. BMI < 18.5 kg/m2 or > 35.0 kg/m^2.
7. Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer), which has an impact on CYP2A6 activity.
8. Subject has a positive serology test for HIV 1/2, Hepatitis B or Hepatitis C.
9. Subject has a history of alcohol abuse that could interfere with the subject's participation in study.
10. Subject has a positive urine drug test. If positive for cannabinoids, inclusion will be at the discretion of the Investigator.
11. Subject has a positive alcohol breath test.
12. Subject or one of their family members [a] is a current or former employee of the tobacco industry.
13. Subject or one of their family members [a] is employee of the investigational site or of any other parties involved in the study.
14. Subject has participated in another clinical study within 30 days prior to the Screening Visit.

15. Subject has been previously screened or enrolled in this study.
16. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding.
17. For women of childbearing potential only [b]: subject does not agree to use an acceptable method of effective contraception. [c]
18. Use of estrogen-containing hormonal contraception or hormone replacement therapy.

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

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

c. Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception without estrogens, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-Up Period.

Investigational Products; Dose; and Mode of Administration:

The 2 variants of P4M3 Gen 2.0 will be provided by the Sponsor. The distribution will be controlled by the Investigator or a qualified and appropriately trained designee.

The following P4M3 Gen 2.0 e-liquid formulations (variants) will be investigated:

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

Subjects' usual brand of cigarettes will be used as comparator. Subjects' preferred brand of commercially available, regular or mentholated cigarettes will not be provided by the Sponsor. All eligible subjects will be asked to purchase their usual brand of cigarettes prior to Admission (Day -1). Every subject needs to bring his/her pack of unopened, single-brand cigarettes.

Duration of Study:

The entire study per subject will last up to 34 days. This will include a screening period of up to 28 days prior to Admission (Day -29 to Day -2), 3 days of confinement (after enrollment on Day -1 to time of discharge on Day 3, (3 overnight stays), and a 3-day Safety Follow-Up (from time of Discharge at Day 3 until Day 6). The end of the study (EOS) for a subject is defined as the end of the Safety Follow-up Period. The end of the whole study corresponds to the individual EOS of the last subject.

Statistical Methods:

Demographics and baseline characteristics will be analyzed on the randomized and PK populations.

PK, PD, HPT and extent of product use endpoints will be analyzed on the randomized and the PK population.

Safety will be analyzed using the safety population.

Nicotine PK endpoints will be derived from the background-corrected plasma nicotine concentrations. Nicotine PK parameters will be derived from background-corrected plasma nicotine concentration versus time data using a non-compartmental analysis (NCA) technique.

All data will be presented in listings, ordered by subject, study visit, product and time point, unless otherwise specified.

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, first and third quartiles, minimum and maximum.

For log normally distributed endpoints, geometric mean, geometric CV and geometric CI will be presented in addition.

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

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

All analyses and summaries will be performed by product.

A mixed model analysis of variance (ANOVA) will be conducted on $AUC_{0\text{-}2min}$, $AUC_{0\text{-}4min}$, $AUC_{0\text{-}Tmax}$, $AUC_{0\text{-}10h}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}infinity,\ max}(C_t/t)_{t\in]0,Tmax]}$ and C_{max} endpoints in the natural logarithmic scale. The results of this analysis will be presented in terms of geometric least square mean ratios and 95% confidence intervals (95% CI) for the P4M3 Gen 2.0: cigarettes ratio and the ratios of variants of P4M3 Gen 2.0.

The analysis of T_{max} will be conducted using non-parametric tests and Hodges-Lehmann estimates of median difference with its derived 95% CI.

Sample Size:

The sample size is empirically based as there are no considerations for statistical hypothesis.

A total of 36 subjects is expected to be sufficient to obtain a precision of 0.55 or less on the P4M3 Gen 2.0 : cigarettes C_{max} ratios.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ABOUT	Assessment of Behavioral OUtcomes related to Tobacco and nicotine products
AE	Adverse event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
$AUC_{0\text{-}2min}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 2 minutes after T_0
$AUC_{0\text{-}4min}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 4 minutes after T_0
$AUC_{0\text{-}Tmax}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to subject-specific time to maximum plasma concentration after T_0
$AUC_{0\text{-}10hours}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 10 hours minutes after T_0
$AUC_{0\text{-}last}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to time of last quantifiable concentration
$AUC_{0\text{-}infinity}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 extrapolated to infinity
BMI	Body mass index
CA35	P4M3 Gen 2.0 variant Classic Auburn 3.5% nicotine
CDC	Centers for disease control and prevention
CM35	P4M3 Gen 2.0 variant Classic Menthol 3.5% nicotine
C_{max}	Background-corrected maximum concentration
CI	Confidence interval
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 (documentation)	Curriculum vitae
CV (statistics)	Coefficient of variation
CYP2A6	Cytochrome P450 2A6
DMP	Data management plan
ECG	Electrocardiogram
E-cigarette	Electronic cigarette
ENDS	Electronic nicotine delivery system
EOS	End of study
FDA	US Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
HPT	Human puffing topography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification

$_{max}(C_t/t)_{t\in]0,Tmax]}$	Maximum ratio of background-corrected concentration over time, from T_0 (excluded) to T_{max} (included) [$_{max}(C_t/t)_{t\in]0,Tmax]}$]
MDEDR	Miniaturized detachable external data recorder
MedDRA	Medical dictionary for regulatory activities
NCA	Non-compartmental analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
PMP	Philip Morris Products S.A.
QC	Quality control
SAE	Serious adverse event
SAP	Statistical analysis plan
SHM	Sample handling manual
SOP	Standard operating procedure
T	Time point
T_0	Time point of the start of product use
$t_{½}$	Half-life
$t_{½z}$	Terminal half-life
T_{max}	Time to background-corrected maximum plasma nicotine concentration
uC	uncorrected nicotine concentration (at T_0: uC_0)
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual Analog Scale
WHO	World Health Organization

Explanation of Terms

Alternates	Subjects who signed the ICF, met the inclusion and exclusion criteria, were enrolled but are not randomized due to a sufficient number of subjects are already randomized. Alternates will be discontinued from the study prior to randomization and will enter the 3-day Safety Follow-Up Period.
End of Study	The end of the study (EOS) for a subject is defined as the end of the Safety Follow-up Period. The end of the whole study corresponds to the individual EOS of the last subject.
Cigarette	The term 'cigarette' refers to manufactured and commercially available regular or menthol cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
Enrollment	At Admission (Day -1) for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily assessed and met.
Randomization	Assignment to the respective sequence of P4M3 Gen 2.0 use and cigarette smoking at Admission (Day -1).
Screen failure	Subject who signs the ICF but is not enrolled at Admission (Day -1).

1 ETHICS AND REGULATIONS

1.1 Independent Review Board (IRB) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] including the subject information sheet, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's brochure [IB], available safety information, curriculum vitae of the Investigator(s) and designee(s) 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 according to the appropriate provisions found in 21 Code of Federal Regulations (CFR) part 50 ("Informed Consent of Human Subjects") and 21 CFR part 56 ("Institutional Review Boards"). The IRB shall be appropriately constituted and perform its functions in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Good Clinical Practice (GCP) [1] and local requirements, as applicable.

In accordance with GCP and 21 CFR part 56, a written confirmation of the IRB approval should be provided to the Sponsor. This should identify the study (name of the Investigator(s) and designee(s), 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, will 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 a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB.

Any change or addition to this protocol will require a written protocol amendment that must be signed by the Sponsor and the Investigator(s). 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(s) 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(s), and is implemented for safety reasons, the Sponsor and the IRB should be informed immediately. The Investigator(s) is(are) responsible for local reporting (e.g., to the IRB) of serious adverse events (SAEs) that occur during the study, according to local regulations.

Relevant safety information will be submitted to the IRB during the study in accordance with national regulations and requirements. Medically qualified study personnel will be available during the study.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [2] and are consistent with the principles of ICH/GCP [1].

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

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

Before or at Screening, the Investigator or designee 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 the necessary information, and if he/she agrees to participate, this will be documented in the ICF by the date and signature of both the subject and the Investigator who conducted the informed consent discussion during Screening Visit. Any procedures specifically described in and related to the study protocol and study conduct, will not be performed before the ICF has been signed. The exact date and time of ICF signature will be captured in the volunteers' registration log.

The personally signed and dated original ICF(s) must be kept by the Investigator and filed in the Investigator study file at the site or with the subject's files and a copy must be given to the subject. The subject will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed, unless he/she refuses in writing. The subject will be informed that additional data analysis not mentioned in the protocol or in the statistical analysis plan (SAP) might be performed with the collected data at a later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.3.2 Amendment to the Informed Consent Form

If a protocol amendment is required, or if any new information regarding the risk profile of the investigational product (IP) becomes available for any other reason deemed necessary, an

amendment to the ICF may be required. If a revision of the ICF is necessary, the Investigator(s) or designee will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a responsible IRB before subjects are required to re-sign the ICF (including date and time). If new and important safety information is received, subjects who already completed or have been discontinued from the study will be informed by letters, emails or phone calls.

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 and designee abide by the principles of the ICH GCP Guideline [1]. These guidelines apply specifically to pharmaceutical development, but nevertheless provide a robust and ethical framework for conducting a clinical study with products such as P4M3 Gen 2.0. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki [2].

In addition, the Investigator or designee 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 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette smoking causes pulmonary, cardiovascular and other serious diseases in smokers [3]. There is no safe cigarette, and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers decide to continue smoking. The development of novel tobacco and nicotine containing products with the potential to be less harmful than cigarettes represents an approach to reduce cigarette-related deaths and diseases among smokers who would have otherwise continued smoking [4]. Philip Morris Products S.A. (PMP) is developing such alternative products that have the potential to reduce individual risk and population harm in comparison to smoking cigarettes. These products aim to substantially reduce or eliminate the exposure to harmful and potentially harmful constituents (HPHCs) generated from cigarette smoke, with the exception of nicotine, while providing an acceptable substitute for cigarettes.

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

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

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

Given that context, when developing new products such as P4M3 Gen 2.0, appropriate assessment including comprehensive understanding of product characterization, its safety, and related impact of product use in humans is critical. P4M3 Gen 2.0 is a closed e-cigarette with a Cartridge that cannot be refilled and for which the e-liquid does not contain THC or Vitamin E acetate (section 2.1.2).

2.1.2 Description of the Product and Scientific Findings

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

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

The aerosol generated by P4M3 Gen 2.0 is free from the majority of HPHCs associated with heating or burning tobacco, except nicotine. P4M3 Gen 2.0 does not contain tobacco and there is no combustion during use.

The non-clinical assessment is described in the Investigator's Brochure and supports the clinical assessment of P4M3 Gen 2.0 [5]. P4M3 Gen 2.0 has not been tested in humans before.

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

When assessing ENDS use, significant inter-subject variability has been described for human puffing topography (HPT) parameters, especially puff duration, puff frequency, and flow rate [6]. Experienced e-cigarette users may extract more nicotine by puffing with a low flow rate and long duration puffs in comparison to cigarette smokers. E-cigarette design features also affect nicotine exposure; increasing the battery voltage output and e-liquid nicotine concentration increases the nicotine delivery [7]. 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 [8]. Battery output, type of wicks, ventilation holes, and other mechanical characteristics of each individual e-cigarette product determine how much aerosol and nicotine is released. More effective and appealing e-cigarette products to provide satisfying alternatives to smoking has led to e-liquids containing 'nicotine salts'. Nicotine salts are formed by the reaction of nicotine with a suitable acid and are less volatile than freebase nicotine [9]. As a result, a greater fraction of the nicotine in the salt form is expected to remain in inhaled aerosol droplets until the aerosol reaches the alveoli for pulmonary absorption.

2.2 Purpose of the Study

The purpose of the study is to evaluate the nicotine pharmacokinetics (PK) profiles of 2 variants of P4M3 Gen 2.0 versus cigarettes following a 6 minutes *ad libitum* use period. In addition, pharmacodynamic effects (PD), including subjective effects and related behavioral assessments, as well as human puffing topography (HPT) will be evaluated, to provide further insights on P4M3 Gen 2.0 product acceptance and product use. Safety will be assessed throughout the study.

The aim is to evaluate if P4M3 Gen 2.0 can provide an acceptable alternative to smoking cigarettes in terms of both, nicotine delivery and sensorial satisfaction for smokers who would otherwise continue smoking cigarettes.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Information on health risks associated with smoking and smoking cessation advice will be provided. Subjects who are motivated to quit smoking or using other nicotine/tobacco-containing products during the study will be given the opportunity to continue their smoking cessation attempt and will be referred to appropriate stop smoking services for continuing support and counselling at a higher level. Subjects who participate in this study will also benefit from repeated and detailed health check-ups.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

The risk of scheduled procedures in the present study (e.g., blood samples) are deemed to be on par with procedures routinely performed during normal or extended health examinations by the subject's healthcare professional. The total volume of blood to be drawn is approximately 300 mL and does not exceed the levels for a standard blood donation. The risks related to blood sampling include for example: excessive bleeding, fainting, hematoma, paresthesia or infection, and those related to the total amount of blood taken over a period of time such as weakness, dizziness or anemia.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product

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

Due to sensorial and technological differences between P4M3 Gen 2.0 and cigarettes, it is possible that subjects will adapt their behavior, e.g., by modifying the number, the volume and/or duration of puffs, as well as the intensity of inhalation.

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

An adult smoker using P4M3 Gen 2.0 may experience:

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

Support during periods of abstinence from any tobacco and nicotine containing products will be provided.

Further risk mitigation will include:

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

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained in detail to study subjects. Unexpected malfunction of the P4M3 Gen 2.0 may lead to unforeseeable risk. Risk mitigation strategies will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 STUDY OBJECTIVES

3.1 Main Objective and Endpoints

The main objective of this study is:

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

   Endpoints (Day 1 to Day 3):

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

3.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

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

   Endpoints (Day 1 to Day 3)

   - Scores from cigarette craving by the visual analog sale (VAS)-craving assessment
   - Score from product evaluation by ABOUT-Product experience questionnaire
   - Score from product liking by the VAS-liking assessment

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

   Related Endpoints (Day 1 to Day 3):

   - Per-puff parameters and per-product use experience parameters from the flight recorder (FR) puffing topography device for 2 variants of P4M3 Gen 2.0 (Appendix D)

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

Related Endpoint (Day 1 to Day 3)

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

4. To evaluate the safety and tolerability during the study

   Related Endpoints (from Enrollment to EOS):

   - Incidence of adverse events (AEs) and serious adverse events (SAEs)
   - Incidence of P4M3 Gen 2.0 product events including malfunction/misuse
   - Changes in physical examination from baseline
   - Changes in electrocardiogram (ECG) from baseline (Heart rate, PR, QRS, QT, QTcF interval)
   - Changes in vital signs from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
   - Concomitant medication
   - Changes in standard spirometry from baseline (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEV_1/FVC)
   - Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel (described in Table 3)

3.3 Exploratory Objectives and Endpoints

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

   Related Endpoints (Day 1 to Day 3)

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

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

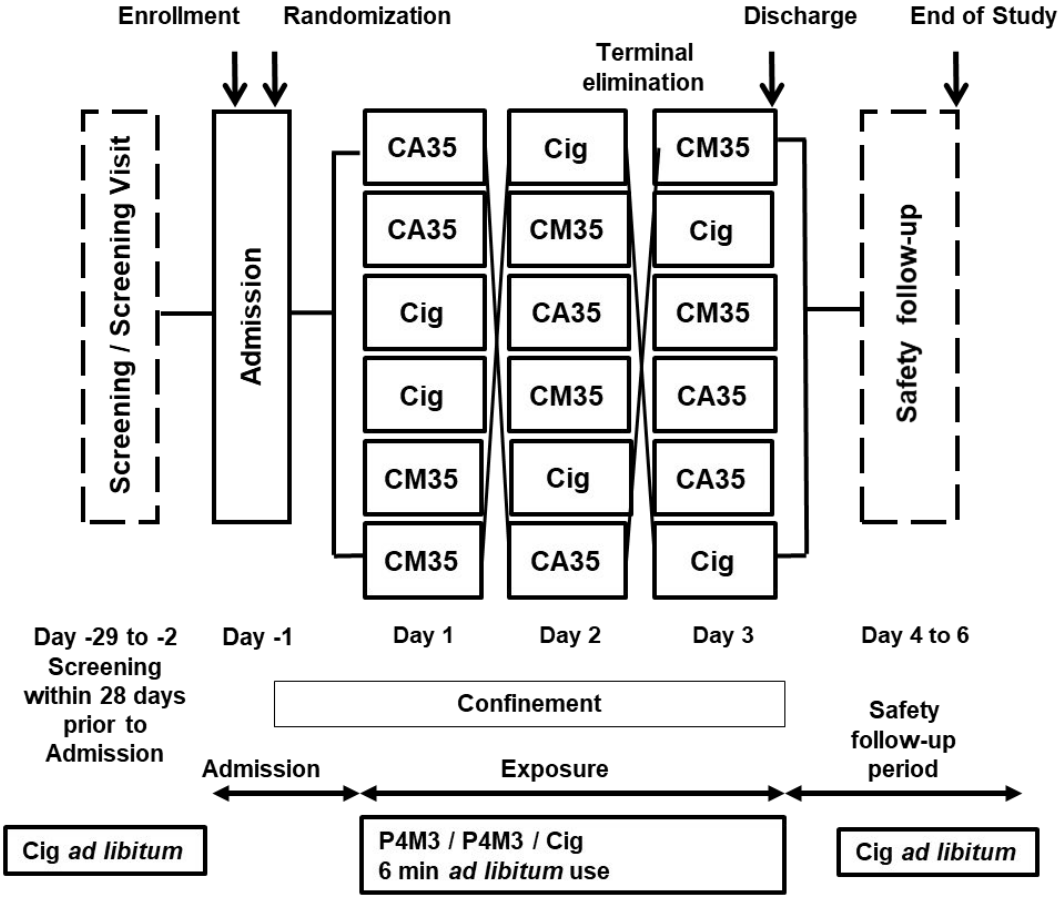
- Serology for human immunodeficiency virus (HIV) 1/2 and hepatitis B and C
- Pregnancy test (all females)
- Urine cotinine test
- Urine drug test including testing for amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates
- Alcohol breath test
- Nicotine dependence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

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

A Screening Visit will be conducted within 28 days (Day -29 to Day -2) prior to Admission (Day -1) to the investigational site (Figure 2). A demonstration of P4M3 Gen 2.0, without product use, will be done by the investigational site staff during the Screening Visit. A sufficient number of subjects will be screened to ensure that 36 subjects will be randomized into the study.



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

Figure 2 Study Design

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

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

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

36 subjects will be randomized to 1 of 6 possible sequences of product use on Day 1 to Day 3 (see Figure 2).

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

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

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

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

Prior to T_0:

- T-1: 5 minutes (± 1 minute)

After T_0:

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

- T10 after 1 hour (± 5 minutes)
- T11 after 2 hours (± 5 minutes)
- T12 after 4 hours (± 5 minutes)
- T13 after 10 hours (± 5 minutes)
- T14 after 24 hours (± 10 minutes) (Day 1 and Day 2 only)

On Day 2, 14 blood samples will be collected for determination of nicotine PK after allocated product use at the same time points, except timepoint T-1. The sample T14 after T_0 on Day 1 will also be used to determine the nicotine baseline concentration prior to T_0 on Day 2 and similarly, T14 after T_0 on Day 2 for nicotine baseline concentration prior to T_0 on Day 3.

On Day 3, 13 blood samples will be collected for determination of nicotine PK after allocated product use. The sample T14 after T_0 on Day 3 will not be collected.

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

Prior to T_0 (for VAS craving assessment only)

- T-15: within 15 minutes prior to T_0 with a time window as indicated in brackets

After T_0: (for VAS craving and VAS liking assessment)

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

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

On Day 2 and 3, additional blood samples will be taken for determination of the nicotine concentration to evaluate terminal elimination half-life ($t_{1/2z}$) in relation to T_0 from Day 2 at the following time points with a time window as indicated in brackets:

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

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

After discharge at Day 3, the subjects will enter a 3-day Safety Follow-Up Period (FU Period) during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs ongoing at discharge will be conducted by the investigational site (section 8.2.6).

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

4.2 Rationale for Study Design

The minimum age of 24 years old in the inclusion criteria was selected based on the legal age of smoking in the United States of America of 21 years; and to account for the 3 years of smoking history.

The goal of this study is to evaluate the nicotine absorption profiles and related PK parameters from two variants P4M3 Gen 2.0 (CA35 and CM35) with 3.5% nicotine compared to cigarettes.

The 6 minutes *ad libitum* use allow appropriate comparisons between different products and smoking a cigarette similar to published data [10-13]. The *ad libitum* use will also allow to explore effects of product liking on PK parameters.

Sampling time points for determination of nicotine concentrations were selected to ensure reliable estimation of PK parameters. In particular, frequent sampling during the first 15 minutes from T_0 will be performed in order to reliably assess T_{max}, which is expected to be comparable to what was observed previously (T_{max} range: 7 to 10 minutes after fixed puffing regimen) with P4M3 Gen 1.0, an earlier developmental version [5] and for cigarettes (T_{max} range: ~10 minutes) [14] and which is compatible with absorption by the pulmonary route.

Comparing early AUC values $AUC_{0\text{-}2min}$, $AUC_{0\text{-}4min}$, $AUC_{0\text{-}Tmax}$, and the maximum ratio $_{max}(C_t/t)_{t\in]0,Tmax]}$ of the 2 variants P4M3 Gen 2.0 and cigarettes may provide insight into the efficiency of nicotine absorption rate into the blood.

The PK of 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 hours [15]. To ensure a complete nicotine washout between each product use, 3 days without product use (cigarette or P4M3 Gen 2.0) would have been required (~ 5 x terminal elimination $t_{1/2z}$). Based on nicotine population PK modeling, it was estimated that nicotine enters in the terminal elimination phase with concentrations decreasing with a terminal elimination rate constant (λ_z) 8 to 10 hours post administration. As a consequence, a minimum of 12 hours has been established in this study design prior to T_0 on Day 1 and approximately 24 hours prior to T_0 on Day 2 and Day 3. Background-concentration correction will be applied to adjust for carry-over effects with adjustment of baseline values to the estimated $t_{1/2z}$ (or λ_z) which will be derived from additional blood sampling on Day 2 and Day 3 for each subject.

The use of estrogen contraceptive is known to accelerate nicotine clearance by 20% to 30% compared to women who do not take estrogen contraceptive [16]. Therefore, for the purpose of this study, use of hormonal contraception containing estrogens is prohibited. This also applies to hormone replacement therapy.

The activity of CYP2A6 will be measured as this enzyme drives the metabolism of nicotine into cotinine and subsequent metabolites. 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 [14].

4.3 Appropriateness of Measurements

All laboratory measures utilized for this study are validated and are appropriate for the study assessments. FTND [17, 18] and ABOUT-Product experience questionnaires [19] used in this study are validated and previously published or adapted versions of validated questionnaires.

4.4 Study Duration

The entire study per subject will last up to 34 days. This will include a screening period of up to 28 days prior to Admission (Day -29 to Day -2), 3 days of confinement (after enrollment on Day -1 to time of discharge on Day 3, 3 overnight stays), and a 3-day Safety Follow-Up (from time of Discharge at Day 3 until Day 6). The end of the study (EOS) for a subject is defined as either the Discharge at Day 3, or the date of early termination of the subject, plus 3 days for the Safety Follow-up Period. The end of the whole study corresponds to the individual EOS of the last subject.

5 STUDY POPULATION

All subjects will undergo a Sars-CoV-2 test according to local regulation and investigational site requirements.

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

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

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

5.1 Selection of Study Population

5.1.1 Inclusion Criteria

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

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

Inclusion Criteria	Screening	Admission (Day -1)
assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, and medical history).		
7. Subject is available for the entire study period and willing to comply with study procedures, including product use assignments, and periods of abstinence from any nicotine/tobacco containing products.	X	X

5.1.2 Exclusion Criteria

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

Exclusion Criteria	Screening	Admission (Day -1)
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).	X	
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners, or subjects who are involuntarily incarcerated).	X	
3. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease) or any other medical condition (including safety laboratory as per CTCAE), which as per the judgment of the Investigator would jeopardize the safety of the subject.	X	
4. As per the Investigator's judgment, the subject has medical conditions which require or will	X	

Exclusion Criteria	Screening	Admission (Day -1)
require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.		
5. Subject has donated or received whole blood or blood products within 3 months prior to Screening Visit.	X	
6. BMI < 18.5 kg/m2 or > 35.0 kg/m^2.	X	
7. Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission, whichever is longer, which has an impact on CYP2A6 activity.		X
8. Subject has a positive serology test for HIV 1/2, Hepatitis B or Hepatitis C.	X	
9. Subject has a history of alcohol abuse that could interfere with the subject's participation in study.	X	
10. Subject has a positive urine drug test. If positive for cannabinoids, inclusion will be at the discretion of the Investigator.	X	X
11. Subject has a positive alcohol breath test.	X	X
12. Subject or one of their family members[a] is a current or former employee of the tobacco industry.	X	
13. Subject or one of their family members[a] is employee of the investigational site or of any other parties involved in the study.	X	
14. Subject has participated in another clinical study within 30 days prior to the Screening Visit.	X	

Exclusion Criteria	Screening	Admission (Day -1)
15. Subject has been previously screened or enrolled in this study.	X	
16. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding.	X	X
17. For women of childbearing potential only[b]: subject does not agree to use an acceptable method of effective contraception [c].	X	X
18. Use of estrogen-containing hormonal contraception or hormone replacement therapy.	X	X

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

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

c. Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception without estrogens, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-Up Period.

5.2 Discontinuation of Subjects from the Study

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

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

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

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

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

- Withdrawal of informed consent.
- Any AE/SAE or condition (including clinically significant changes in a laboratory parameter), which at the discretion of the Investigator is not compatible with the subject's continued participation in this study.
- Positive pregnancy test (section 8.5).
- The Sponsor the study. If the Sponsor decides to prematurely terminate the study, the subject will be promptly informed by the Investigator. The Investigator should report the fact and the reason in writing to the IRB.
- Discontinuation is considered to be in the best interest of the subject, or the other subjects as judged by the Investigator
- Subject is not willing and/or ready to use P4M3 Gen 2.0 after the product test at Admission (Day -1). In such a situation, the subject will be discontinued after the product test and will enter the 3-day Safety Follow-up.
- Subject uses any tobacco or nicotine containing product different from the assigned product during confinement.

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

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

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

5.3 Lost to Follow-up

A reasonable number of attempts to contact the subject should be done and documented in the source documents by the site. When the Investigator declares a subject as lost-to-follow-up, the lost to follow-up date will be recorded. The date of lost to follow-up corresponds to the date of the end of study of the subject.

If the investigational site lost contact to the subject but the subject has reached the maximum number of study days (34 days), then the Investigator or designee(s) will declare the subject lost to follow-up at this date.

5.4 Violation of Eligibility Criteria

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

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

P4M3 Gen 2.0 will be provided by the Sponsor.

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

6.1.1 Test Product

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

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

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

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

The P4M3 Gen 2.0 e-liquid formulations are composed of propylene glycol (PG), vegetable glycerin (VG), water, tobacco-derived nicotine, lactic acid, benzoic acid and could differ in flavors and nicotine concentrations. The following P4M3 Gen 2.0 e-liquid formulations (variants) will be investigated in this study (Table 1).

Table 1 P4M3 Gen 2.0 variants

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

The non-clinical assessment is described in the Investigator's brochure and supports the clinical assessment of P4M3 Gen 2.0 [5].

6.1.2 Reference Product / Baseline Product

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

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

6.1.3 Packaging and Labeling

At Admission (Day -1), all study subjects will provide one sealed pack of cigarettes to the investigational site staff. The cigarette pack provided by the subject should not be opened and the cellophane should be intact.

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

For P4M3 Gen 2.0, packs of P4M3 Gen 2.0 Cartridges will be printed with the necessary information including, but not limited to, product code and expiry date.

6.2 Use of Investigational Product(s)

Subjects will not be forced to smoke cigarettes or use P4M3 Gen 2.0 and will be free to stop smoking/using tobacco/nicotine-containing products at any time of the study.

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

6.2.1 Admission (Day -1)

After enrollment in the study, subjects will be provided with information on the risks of smoking, advice on smoking cessation and briefing on P4M3 Gen 2.0 and will perform a product test with P4M3 Gen 2.0 (with CA35 only) for a maximum of 10 minutes. After the product test, subjects willing and ready to use P4M3 Gen 2.0 during the study will be required to abstain from any nicotine/tobacco containing product use until the first product use on Day 1.

6.2.2 Exposure Period (Day 1 and Day 3)

On Day 1 to Day 3, after at least 12 hours of abstinence from any tobacco/nicotine containing products, subjects will start using their allocated product *ad libitum* for 6 minutes ± 30 seconds (section 4.1).

For P4M3 Gen 2.0 use, subjects will be provided with a new P4M3 Gen 2.0 Cartridge (CA35 or CM35 depending on product assignment) and a fully charged P4M3 Gen 2.0 Battery unit with the MDEDR puffing topography device connected.

For cigarette smoking, subjects will smoke one cigarette *ad libitum* for 6 minutes ± 30 seconds.

6.2.3 Discharge (Day 3)

After Discharge, subjects will be free to use any nicotine/tobacco products according to their usual habits.

6.2.4 Safety Follow-up Period

During the 3-day safety follow-up period, subjects will be free to use any nicotine/tobacco containing products according to their usual habits.

6.2.5 Stopping Rules for Investigational Products

For safety purposes, using P4M3 Gen 2.0 or smoking cigarettes should be temporarily 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 9.7), unless they disagree or certain procedures have already been performed (section 5.2).

6.3 Method for Assigning Subjects to Product Sequences

On Day -1, the subjects will be randomized to one of the six sequences of the 3-period cross-over design (section 4.1) by means of a permuted-block schema. Details about the randomization process will be included in the Data Management Plan (DMP).

The following quotas will be applied on the total number of randomized subjects:

- At least 40% of each sex will be represented
- At least 15% of Black, Asian, American Indian or Alaska native, Native Hawaiian, and other Pacific Islander race will be represented

If a sufficient number of subjects are already randomized to the study sequences, any additional subjects (alternates) will be discontinued from the study prior to randomization and will enter the 3-day Safety Follow-Up Period (section 5.2).

Block size and other randomization details will be available in the randomization plan. The randomization scheme will be generated by an independent statistician and neither the Sponsor staff, nor Investigator or study subjects will have access to the randomization scheme during study conduct.

6.4 Blinding

This is an open-label study. Therefore, the subjects, the Investigator, the PMP and CRO personnel will be unblinded to the subject's sequence and product use.

6.5 Investigational Product Accountability and Compliance

6.5.1 Dispensing Investigational Product

From Day -1 until Day 3, P4M3 Gen 2.0, comprising of a fully charged Battery unit with a full Cartridge, and cigarettes will be dispensed by the investigational site staff, as per the study design. For each product use, subjects will receive a full Cartridge.

Each dispensing of investigational products to the subject will be recorded in a log.

6.5.2 Storage and Accountability

P4M3 Gen 2.0 components and cigarettes will be stored in a secured storage place at the investigational site with access limited to the authorized personnel only. The distribution and return of investigational products will be controlled by qualified and appropriately trained investigational site staff. Subjects will return P4M3 Gen 2.0, comprising of the P4M3 Gen 2.0 Battery unit and the P4M3 Gen 2.0 Cartridge, immediately after the 6 minutes *ad libitum* use

to the investigational site staff for accountability and P4M3 Gen 2.0 Cartridge weighing (section 7.8.3).

Smoked cigarettes will be documented and cigarette butts will be collected by investigational site staff.

6.5.3 Investigational Product Retention

Used and unused P4M3 Gen 2.0 Battery units and P4M3 Gen 2.0 Cartridges will be destroyed or returned to the Sponsor upon study completion. Smoked cigarette butts will be destroyed upon study completion.

6.5.4 Compliance to Investigational Products

Compliance will be ensured by strict distribution and collection of any used and unused P4M3 Gen 2.0, comprising of the P4M3 Gen 2.0 Battery unit and the P4M3 Gen 2.0 Cartridge, and cigarettes / cigarette butts by designated investigational site staff.

6.6 Restrictions

6.6.1 Smoking Restrictions

During the Screening period, subjects will be allowed to use any nicotine/tobacco-containing products according to their usual habits except during the procedures of the Screening Visit (section 9.1). Spirometry assessments at Screening and at Day -1 will be performed 1 hour after stopping smoking (section 9.1 and 9.2).

From Admission (Day -1) to Discharge (Day 3) or early termination, use of any nicotine/tobacco containing products, except use as per study design of the allocated product will not be permitted.

A nicotine washout period of at least 12 hours should be respected before product use at Day 1 to Day 3.

6.6.2 Dietary Restrictions

A standard diet will be designed for the whole confinement period. For each meal, the caloric and fat content should be controlled to avoid a “high-fat” diet. The FDA guidance on food-effect studies for bioequivalence testing identifies a “high-fat” diet as a diet which contains “approximately 50 percent of total caloric content of the meal [from fat] and is high in calories (approximately 800 to 1000 calories) [20].”

Subjects are not allowed to bring their own food or beverages to the investigational site. Meals will be served as described in section 9. Additional light snacks, fruits, and raw vegetables can be distributed to the subjects without restrictions at any time during confinement (except during product use periods) if they comply with the standard diet. Consumption of water is allowed as desired. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed. Subjects should refrain from ingesting foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade from 7 days prior to Day -1 and throughout the study. The same menu and meal schedule will be administered uniformly for all subjects. Subjects should have fasted (black coffee or tea without sugar is possible) for at least 6 hours prior to safety laboratory assessments at Day -1 and on Day 3.

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

6.7 Concomitant Medication

All medication taken within 4 weeks prior to the ICF signature will be considered prior medication. All medication taken from Screening Visit to end of the Safety Follow-Up Period will be considered concomitant medication.

Only progesterone-containing hormonal contraception will be allowed. Hormonal contraception containing estrogens or hormone replacement therapy will be prohibited and subjects will be excluded based on eligibility criteria.

Any medication with an impact on the CYP2A6 metabolism [21] (used as prescription and over-the-counter products), including, but not limited to medications listed in Table 2, must be avoided as CYP2A6 is involved in the nicotine metabolism. To be eligible for the study, any medication with impact on CYP2A6 metabolism must have been discontinued at least 14 days prior to Day -1 or for at least 5 half-lives (whichever is longer). It is at the discretion of the Investigator to assess if a termination of such medication is medically justified and safe for the subject. In addition, they should not be used during the entire study until the time of Discharge or early termination. Prior to database lock, concomitant medication will be reviewed for their potential impact on CYP2A6 activity and the study results.

Table 2 CYP2A6: Substrates, Inhibitors, and Inducers

Inhibitors	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
Inducers	**Drug Class**
Amobarbital	Barbiturate
Pentobarbital	Barbiturates
Phenobarbital	Barbiturates/anticonvulsants
Rifampin	Antimycobacterials
Secobarbital	Barbiturates
Substrates	**Drug Class**
Dexmedetomidine	α_2-Adrenoceptor, sedative
Ifosfamide	Anti-cancer, alkylating agents

Use of over-the-counter medication will be restricted from Admission (Day -1) to Discharge or early termination, although exceptions may be made on a case-by-case basis at the discretion of the Investigator.

Use of any other concomitant medication will be evaluated on a case-by-case basis by the Investigator. Any concomitant medication used will be fully documented (section 7.4.2).

7 STUDY PROCEDURES

Investigational site staff performing or recording study assessments must have the appropriate and fully documented training. An overview of study assessments and time points is shown in the schedule of events (Appendix A). Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care. Site personnel will adhere to the site's standard operating procedures (SOPs) for study related procedures.

7.1 Informed Consent

Subjects will be asked to provide their written consent to participate in the study (section 1.3). Study assessments must only start after the time of ICF signature by the subject.

7.2 Information on the Risk of Smoking and Smoking Cessation Advice and Debriefing on P4M3 Gen 2.0

At the Screening Visit, before enrollment at Day -1 and at Discharge (Day 3), subjects will receive 1) information on the risks of smoking, 2) smoking cessation advice, and 3) debriefing on P4M3 Gen 2.0 as described in the Schedule of events (Appendix A).

The information on the risk of smoking and advice on smoking cessation will take the form of a brief interview according to the WHO recommendations [22]. The debriefing of subjects on P4M3 Gen 2.0 will address any intended or unintended beliefs that subjects may have about P4M3 Gen 2.0. The goal of the debriefing is to help ensure that subjects enter and exit the study with an accurate understanding of the product risks.

Details of the sessions will be recorded in the source document file. This information will be given to the subjects on an individual basis during a face-to-face meeting between the subject and the Investigator or may be given in a group session.

7.3 Support during Abstinence from any Tobacco and Nicotine Containing Products

Subjects will be offered support during periods of abstinence from any nicotine/tobacco containing products during the study from Day -1 to Discharge by the Investigator and/or investigational site staff as per Schedule of events. Support resources will include counselling and assistance, entertainment, monitoring of the subject's behavior, AEs, and the subject's mood, clinical tests e.g., vital signs, physical examination.

7.4 Clinical Assessments

7.4.1 Demographic Data

Sex, date of birth, race and ethnicity will be recorded for each subject as described in the Schedule of events.

7.4.2 Medical History, Concomitant Disease, Prior and Concomitant Medication

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

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

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

7.4.3 Physical Examination

Physical examinations will be conducted as described in the Schedule of events.

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

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

7.4.4 Body Height and Weight and BMI

Body height and weight will be recorded at the Screening Visit and body-mass-index (BMI) will be calculated using the following formula:

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

The BMI will be used to assess eligibility for enrollment.

7.4.5 Vital Signs

Vital signs (systolic and diastolic blood pressure, respiratory rate and pulse rate) will be measured as described in the Schedule of events. On Day 1 to Day 3, vital signs will be assessed prior to T_0.

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

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

7.4.6 Spirometry

Spirometry without bronchodilator will be performed at the Screening Visit, Day -1 and at Discharge (Day 3) or early termination in accordance with the 2005 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry [23, 24]. Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set [25].

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

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

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

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

7.4.7 Electrocardiogram

At the Screening Visit, Day -1 and at Discharge (Day 3) or early termination, a standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position as described in the Schedule of events.

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

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

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

7.5 Biomarker Assessment

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

7.5.1 Biomarkers of Exposure to Nicotine

On Day 1 to Day 3, venous blood samples will be collected to evaluate nicotine plasma PK profile and at Day 2 and Day 3 additional samples will be collected for determination of terminal elimination half-life as described in the Schedule of events.

The time of collection of each blood sample must be recorded on the CRF.

7.5.2 CYP2A6 Activity

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

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

The time of collection of the blood sample must be recorded on the CRF.

7.6 Laboratory Assessments

7.6.1 Clinical Chemistry, Hematology, and Urine Analysis Safety Panel

Hematology and clinical chemistry analysis will be assessed as per Schedule of events. Subjects should have fasted for at least 10 hours prior to safety laboratory assessments, except at Screening and early termination where non-fasting samples can be used. Tests will be conducted at a local laboratory (Appendix B). If during the screening period a blood sample is not suitable for analysis (e.g., blood clotting) a re-test should be performed for the specific parameters which are not available. Safety urine analysis will be assessed at Screening, Admission and at Discharge or at early termination.

Parameters to be tested are listed in Table 3.

Table 3 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 (WBC) cell count • Differential WBC count: - Neutrophils - Basophils - Eosinophils - Lymphocytes - Monocytes	• Albumin • Total protein • Alkaline phosphatase • Alanine aminotransferase • Aspartate aminotransferase • Blood urea nitrogen • Creatinine • Gamma-glutamyl transferase • Glucose • Lactate dehydrogenase • Potassium • Sodium • Total bilirubin • Direct bilirubin • Total cholesterol • Triglycerides	• pH • Bilirubin • Glucose • Nitrite • Red blood cell traces • Protein • Specific gravity

7.6.2 Serology

Tests for hepatitis B (HbsAg), hepatitis C (HCV antibody) virus and human immunodeficiency virus (anti-HIV1/2) will be performed at the Screening Visit.

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In case of positive results, the subject will be referred to appropriate medical care.

7.6.3 Urine Drug Test

A urine drug screen including testing for alcohol will be performed at the site at the Screening Visit and at Day -1. The urine will be screened for:

- amphetamine type substances,
- barbiturates,
- benzodiazepines,
- cannabinoids,
- cocaine,
- opiates, and

In case of a positive urine drug test, a re-test will not be allowed in order to evaluate eligibility. In case of an inconclusive test, a re-test can be performed but this needs to be done immediately after the inconclusive test. If positive for cannabinoids, a cannabis intoxication evaluation will be performed at Screening and at Admission and inclusion will be at the discretion of the Investigator.

7.6.4 Urine Cotinine Test

A urine cotinine test will be performed to confirm the nicotine/tobacco use status as described in the Schedule of events.

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

7.6.5 Urine Pregnancy Test

A urine pregnancy test will be performed for all female subjects as per Schedule of events. Subjects with a positive urine pregnancy test or unclear results (from two repetitions) before enrollment will be considered as screen failures. In case of any positive pregnancy test, the

Investigator or designee will inform the subject about the risks associated with smoking during pregnancy and subjects will be referred to health care facility/health care provider for pregnancy follow-up.

All pregnancies detected during the study must be reported and handled as described in section 8.5. Pregnancies detected after enrollment will lead to discontinuation from the study (section 5.2).

7.6.6 Alcohol Breath Test

An alcohol breath test will be performed in all subject as described in the Schedule of events.

7.7 Sample Handling, Storage, and Shipment

Urine drug test including testing for alcohol, urine pregnancy tests and urine cotinine tests will be done by the site personnel at the site. All other blood and urine samples will be managed by the laboratory designated in Appendix B.

Detailed procedures for handling of samples are described in the separate sample handling manual (SHM). Safety laboratory samples will be destroyed as per laboratory local regulations. All other samples will be destroyed post database lock or post finalization of the bioanalytical reports, whichever occurs 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.

7.7.1 Blood Samples

Blood samples will be drawn by qualified and trained site personnel and according to the standard operating procedures (SOPs) at the investigational site.

Since the test for nicotine concentration is highly sensitive, precautions should be taken during blood sampling and processing to prevent the contamination of samples with environmental nicotine.

In total, approximately 300 mL of blood will be collected for this study including samples for determination of plasma nicotine concentrations (approximately 230 mL), CYP2A6 activity (5 mL), serology (5 mL) and safety laboratory (approximately 60 mL). This calculation is based on an individual volume of each sample of 5.0 mL for nicotine PK, 5.0 mL for CYP2A6 analysis, 5 mL for serology, 20 mL per safety laboratory assessments. The total volume of blood drawn will not exceed the levels for a standard blood donation.

Details on the procedures for collection, labeling, handling and shipment of samples are described in the SHM/ laboratory manual.

7.8 Other Study Procedures

7.8.1 Demonstration and P4M3 Gen 2.0 Product Test

All subjects will have a demonstration of P4M3 Gen 2.0 by the investigational site staff at the Screening Visit without product use.

At Admission (Day -1), after enrollment, investigational site staff will inform subjects on product use and subjects will have a product test with P4M3 Gen 2.0 with CA35 Cartridge *ad libitum* for up to 10 minutes.

7.8.2 Human Puffing Topography

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

The MDEDR puffing topography device measures and records the flow rate and other per-puff parameters listed in Appendix D. From the per-puff parameters, per-product experience parameters, representing average or total values per product, will be derived (Appendix D).

The MDEDR puffing topography device will be used with the P4M3 Gen 2.0 on Day 1 to Day 3 with data recording during 6 minutes (±30 seconds) *ad libitum* use as described in the Schedule of events. Data will be not be collected during cigarette smoking.

The P4M3 Gen 2.0 device is equipped with a pressure sensor, which measures the pressure at the Cartridge level. When a puff is drawn, the P4M3 Gen 2.0 calculates the difference of pressure between the atmospheric pressure and the pressure measured at the Cartridge level. The aerosol production (heating cycle) is then triggered based on the difference of pressure values calculated by the device. The MDEDR puffing topography device is mechanically attached to the Battery unit of P4M3 Gen 2.0 and electronically connected to its USB port. The MDEDR puffing topography device works as a data logger. Once connected to the P4M3 Gen 2.0 device, the MDEDR puffing topography device is able to record HPT data. Any malfunction of the MDEDR puffing topography device will be documented in the appropriate log.

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

Prior to calculation of the per-product experience parameters, the Sponsor's HPT group will process, validate and discard any invalid data, as per the Sponsor's SOPs. The Sponsor will

provide copies of both the raw and validated HPT datasets to the Investigator. Only valid data for the per-puff and per-product use experience parameters will be part of the study database and will be analyzed.

7.8.3 Weighing of P4M3 Gen 2.0 Cartridge

P4M3 Gen 2.0 Cartridges will be weighed before T_0 and within 120 min after T_0 as described in the Schedule of events to estimate the amount of nicotine delivered during product use.

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

7.9 Questionnaires

The questionnaires will be asked to the subject as described in the Schedule of events (Appendix A) and will be completed by the subjects. All subject-reported outcome as well as instructions will be provided in the subject's local language.

7.9.1 Fagerström Test for Nicotine Dependence (FTND, Revised Version)

At the Screening visit, potential nicotine dependence will be assessed as per Schedule of Event using the FTND in its revised version [18] as updated in 2012 [26].

The questionnaire consists of six questions which have to be answered by the subject himself/herself. The scores obtained on the test permit the classification of nicotine dependence into three levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points) [26].

7.9.2 Nicotine/Tobacco Product Use History

At the Screening Visit, subjects will be asked questions about their tobacco-and/or nicotine-containing products use history. The questions will capture frequency and quantity of tobacco and/or nicotine-containing product use over the past 4 weeks, and number of continuous years of cigarette smoking. This information will be used as characteristics of the study subjects and to assess their eligibility to participate in the study.

7.9.3 ABOUT-Product Experience Questionnaire

Product experience will be assessed via a subject self-reported outcome measure, part of the ABOUT toolbox [27, 28].

The questionnaire consists of 3 multi-item scales and 2 single-item scales, arising from an adaptation and rewording of the modified cigarette evaluation questionnaire (mCEQ) [19] to RRPs and the Product Evaluation Scale [29].

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

- Product satisfaction (satisfying, tastes good, enjoy the product).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nausea).
- Enjoyment of respiratory tract sensations (single-item assessment).
- Craving reduction (single-item assessment).

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

7.9.4 VAS Craving Assessment

Cigarette craving will be assessed using a 1 item self-reported craving VAS [30], asking subjects to rate craving for cigarettes (*How strong is your craving for cigarettes?),* on a 100 mm unipolar scale, ranging from 0 (no craving), to 100 (strong craving).

7.9.5 VAS Liking Assessment

Cigarette and P4M3 Gen 2.0 liking will be assessed using a one item self-reported liking VAS, asking subjects to rate liking for product *(At this moment, my liking for this product is:)* on a 100 mm bipolar scale, ranging from 0 (strong disliking), to 100 (strong liking), with a neutral middle point, as recommended in the FDA guidance for industry on abuse liability assessment [31].

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

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

8.1.2 Serious Adverse Events

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

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

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

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

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

Clinical conditions that existed before the start of the period of collection of AEs and are still ongoing at Screening (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 the start of the collection period. Otherwise, any medical condition that existed before the start of the period of collection and still ongoing at Screening (concomitant disease) and whose severity increased after that point is to be captured as an AE or SAE, depending on the seriousness criteria met.

8.2 Collection and Reporting of Adverse Events

8.2.1 Collection of Information

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

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

Information recorded will include: verbatim description of the AE/SAE, start and stop dates and times, 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, stabilized,).

Information to be recorded about an AE/SAE should 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

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

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

During a 3-day Safety Follow-Up Period new AEs/SAEs will be recorded and ongoing AEs/SAEs will be followed-up by the study site. In general, 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 or subject is lost to follow up. Any AEs or SAEs that are ongoing at the end of the Safety Follow-Up Period will be managed as described in section 8.2.6.

8.2.3 Intensity of Adverse Event

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

Table 4 Intensity of Adverse Events

Mild:	Easily tolerated, not interfering with normal everyday activities
Moderate:	Interferes with normal everyday activities, but the subject is still able to function
Severe:	Incapacitating and requiring medical intervention

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

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

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

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

8.2.5 Expectedness

Any AE assessed as related to the IP (P4M3 Gen 2.0 or cigarettes) will be assessed for its expectedness. An AE will be regarded as "unexpected" if its nature or severity is not consistent with information already recorded in section 6.5 of the current Investigator's Brochure [5].

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

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

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

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

8.3 Reporting of Serious Adverse Events

Any SAE observed during the period of collection in this study must be reported within 24 hours of first awareness to Sponsor, via email, having the SAE form attached as detailed in the Safety Management Plan (SMP).

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

The 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 IRB, according to local regulations and in accordance with the respective safety management plan (SMP).

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 Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grading scales (Appendix C). 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 as described in 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 either be recorded as AEs (and handled as described in section 8.2) or linked to a concomitant disease or to an already reported AE.

The principles for assessing and reporting abnormal laboratory test results, emerging after the Screening Visit, using CTCAE 5.0 grading scales are set up in Table 5:

Table 5 Principles for Assessing and Reporting Abnormal Laboratory Test Results

Grading	Clinically significant?	Is it a grade increase 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.

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

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

8.5 Reporting and Follow–Up of Pregnancies

8.5.1 Period of Collection and Follow-up

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

In case of pregnancies detected between enrollment and prior to randomization, subject will be discontinued, and reported as "enrolled but not randomized" subject. Early termination procedures shall apply. No pregnancy form will be filled.

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

Any pregnancy that was potentially associated with exposure to IP (P4M3 Gen 2.0 or cigarette) will be followed-up until an outcome is reached (e.g., normal delivery, spontaneous abortion, or voluntary termination) and also until 8 weeks after delivery. Any pregnancy complication, adverse pregnancy outcome or maternal complications will be recorded as an AE accordingly.

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

8.5.2 Reporting of Pregnancies

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

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the early termination procedures (section 9.7), as soon as practical after discontinuation and will enter the 3-day Safety Follow-Up Period. In general, 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 Safety Follow-Up Period will be managed as described in section 8.2.6.

8.7 Investigational Product Malfunction and Misuse

Any occurrence of P4M3 Gen 2.0 product events, affecting P4M3 Gen 2.0 Battery unit and /or P4M3 Gen 2.0 Cartridge, including malfunction or misuse (use not in accordance with its instruction) by a subject will be documented by the Investigator. Information regarding P4M3 Gen 2.0 product events should be actively collected during the study and assessed for severity as Minor or Major:

Minor – Can be resolved easily.

Major – Cannot be resolved.

P4M3 Gen 2.0 product events will be categorized into: Break, Fluid Leak, Intermittent Loss of Power, Power Problem, Premature Indicator Activation or Other.

Investigational product misuse may result in use-related hazards (section 2.3.4).

Furthermore, any malfunction or misuse of P4M3 Gen 2.0 that leads to an AE/SAE will follow the same processes as described above.

9 STUDY ACTIVITIES

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

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

The main objective for this study is the evaluation of the plasma concentration-time profile of nicotine and derived PK parameters. Therefore, the collection of blood samples for determination of plasma nicotine concentration should be as close to the schedule time as possible and should take precedence over any other assessments required at the same time.

9.1 Screening Visit (Day -29 to Day -2)

The Screening Visit will be performed within 28 days prior to enrollment at Admission (Day -1). First, the ICF along with study information should be given to the subject. Prior to being asked to sign the consent form, subjects will be given time to review the study information and ask any questions. When/if the ICF is signed, dated and timed, the other screening procedures can be performed in the order deemed most practical. While it is recommended to complete as many screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed at the Screening Visit at the discretion of the investigational site.

Screening activities are listed in Table 6.

Table 6 Time Schedule – Screening Visit

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
Prior to any other study procedure		Informed consent process and signature of ICF	
During the visit		Information on the risks of smoking/advice on smoking cessation and debriefing on P4M3 Gen 2.0 Nicotine/Tobacco product use history	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
		FTND questionnaire	
		Demographics data	
		Medical history/ concomitant diseases	
		Prior (within 4 weeks prior to the Screening Visit) and concomitant medication	
		Physical examination	
		Body height, weight and calculated BMI	
		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement. At least 15 minutes abstinence from any nicotine/tobacco containing products prior to measurement.
		ECG	After resting for at least 10 min in supine position prior to recording
		Spirometry	Has to be done at least 1 hour after stopping smoking. After resting in sitting position for at least 15 minutes prior to testing.
		Alcohol breath test	
	✓	Clinical laboratory parameters (hematology, clinical chemistry)	
		Collection of spot urine for: - Urine analysis safety panel - Urine drug test including testing for alcohol - Urine cotinine test - Urine pregnancy test (all female subjects)	
	✓	Serology	HIV 1/2, Hepatitis B and C,
		Review of inclusion/exclusion criteria based on all relevant assessments	Includes willingness to comply with study procedures, including periods of abstinence from any nicotine/tobacco containing

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
			products; intention to quit smoking or using other nicotine/tobacco-containing products in the next 3 months
		P4M3 Gen 2.0 demonstration	Without product use
During the visit		AE/SAE recording	If the Screening Visit is performed on two separate days the AE/SAE questions will be asked again.

Abbreviations:

AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; HIV = Human immunodeficiency virus; SAE = Serious adverse event.

If the inclusion and exclusion criteria are met, the investigational site staff will contact the subject to arrange Day -1 visit at site.

9.2 Admission (Day -1)

The assessments performed at Admission are listed in Table 7.

Table 7 Time Schedule – Admission (Day -1)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Before enrollment		Information on the risks of smoking/advice on smoking cessation and debriefing on P4M3 Gen 2.0	
		Nicotine/Tobacco product use history	
		Concomitant medication/ concomitant disease status check	
		Physical examination	
		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement. At least 15 minutes abstinence from any nicotine/tobacco containing products prior to measurement.
		ECG	After resting for at least 10 min in supine position prior to recording.
		Spirometry	Has to be done at least 1 hour after stopping smoking. After resting in sitting position for at least 15 minutes prior to testing.
		Serology	
		Alcohol breath test	
		Collection of spot urine for: - Urine analysis safety panel - Urine drug test including testing for alcohol - Urine cotinine test - Urine pregnancy test (all female subjects)	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		Re-check of Inclusion criteria 4, 5 and 7 and exclusion criteria 7, 10, 15, 16 and 17.	
		Enrollment	
	✓	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 10 hours of fasting.
		Urine analysis safety panel	
After enrollment	✓	CYP2A6 activity	Before product test
After collection of sample for CYP2A6		P4M3 Gen 2.0 product test with CA35 Cartridge by subject	Up to 10 minutes *ad libitum* use.
During the visit		AE/SAE recording	
During the visit		Product events malfunctions/misuse	

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

9.3 Day 1

The study activities performed on Day 1 are listed in Table 8.

Table 8 Time Schedule – Day 1

Time	Blood Sample	Procedures	Additional Information
Prior to T_0		Weighing of P4M3 Gen 2.0 CA35 and CM35 Cartridge and connection of P4M3 Gen 2.0 to MDEDR HPT device	
Prior to T_0		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.
Within 15 minutes prior to T_0		VAS craving assessment	
5 minutes ± 1 minute prior to T_0	✓	Blood sampling for baseline nicotine level	
Just before T_0		Turning on P4M3 Gen 2.0 or lighting of cigarette	Performed by investigational site staff
Start of product use: T_0		P4M3 Gen 2.0 product use with MDEDR HPT recording Cigarette smoking without HPT recording	After at least 12 hours of nicotine washout.
During/after 6 min *ad libitum* product use	✓	Blood sampling for nicotine PK	Post T_0, blood will be drawn at the following time points: T1 after 1 minute + 30 seconds T2 after 2 minutes + 1 minute T3 after 4 minutes + 1 minute T4 after 6 minutes + 1 minute T5 after 8 minutes + 1 minute T6 after 10 minutes + 1 minute T7 after 12 minutes + 1 minute T8 after 15 minutes ± 2 minutes T9 after 30 minutes ± 2 minutes T10 after 1 hour ± 5 minutes T11 after 2 hours ± 5 minutes T12 after 4 hours ± 5 minutes T13 after 10 hours ± 5 minutes.

Time	Blood Sample	Procedures	Additional Information
			T14 after 24 hours ± 10 minutes (Day 2 baseline)
		VAS craving assessment, VAS liking assessment	Post T_0, assessments will be done at the following timepoints: T1 after 4 minutes ± 1 minute T2 after 10 minutes ± 1 minute T3 after 15 minutes ± 1 minute T4 after 30 minutes ± 2 minutes T5 after 1 hour ± 5 minutes T6 after 2 hours ± 5 minutes T7 after 4 hours ± 5 minutes T8 after 10 hours ± 5 minutes
Within 120 minutes after T_0		Breakfast	
Between 60 minutes and 120 minutes after T_0		ABOUT-Product experience questionnaire	
Within 120 min after T_0		Collection and weighing of used P4M3 Gen 2.0 CA35 and CM35 Cartridges, collection of cigarette buttes	
After at least 4 hours after T_0		Lunch	
During nicotine washout		Nicotine washout	Optional: snacks and water
Ongoing		Support during period of abstinence from any tobacco and nicotine containing products	
Ongoing		AE/SAE, concomitant medication recording/ concomitant diseases status check	
Ongoing		Product events malfunctions/misuse	

Abbreviations: AE = Adverse event; ECG = Electrocardiogram; HPT = Human puffing topography; PK = Pharmacokinetic; SAE = Serious adverse event; VAS = Visual analogue scale

9.4 Day 2

The study activities performed on Day 2 are listed in Table 9.

Table 9 Time Schedule – Day 2

Time	Blood Sample	Procedures	Additional Information
Prior to T_0		Weighing of P4M3 Gen 2.0 CA35 and CM35 Cartridge and connection of P4M3 Gen 2.0 to MDEDR HPT device	
Prior to T_0		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.
Within 15 minutes prior to T_0		VAS craving assessment	
5 minutes ± 1 minute prior to T_0	✓	Blood sampling for baseline nicotine level	Sample T14 after 24 hours ± 10 minutes from T_0 on Day 1
Just before T_0		Turning on P4M3 Gen 2.0 or lighting of cigarette	Performed by investigational site staff
Start of product use: T_0		P4M3 Gen 2.0 product use with MDEDR HPT recording Cigarette smoking without HPT recording Cigarette smoking without HPT recording	After approximately 24 hours of nicotine washout. Within ± 20 minutes of T_0 of prior study day.
During/after 6 min *ad libitum* product use	✓	Blood sampling for nicotine PK	Post T_0, blood will be drawn at the following time points: T1 after 1 minute + 30 seconds T2 after 2 minutes + 1 minute T3 after 4 minutes + 1 minute T4 after 6 minutes + 1 minute T5 after 8 minutes + 1 minute T6 after 10 minutes + 1 minute T7 after 12 minutes + 1 minute T8 after 15 minutes ± 2 minutes T9 after 30 minutes ± 2 minutes T10 after 1 hour ± 5 minutes

Time	Blood Sample	Procedures	Additional Information
			T11 after 2 hours ± 5 minutes T12 after 4 hours ± 5 minutes T13 after 10 hours ± 5 minutes
	✓	Blood sampling for determination of subject's nicotine $t_{1/2z}$	Blood will be drawn at the following time points after T_0 on Day 2: T1z after 8 hours ± 5 minutes T2z after 12 hours ± 5 minutes T3z after 16 hours ± 10 minutes, T4z after 20 hours ± 10 minutes,
		VAS craving assessment, VAS liking assessment	Post T_0, assessments will be done at the following timepoints: T1 after 4 minutes ± 1 minute T2 after 10 minutes ± 1 minute T3 after 15 minutes ± 1 minute T4 after 30 minutes ± 2 minutes T5 after 1 hour ± 5 minutes T6 after 2 hours ± 5 minutes T7 after 4 hours ± 5 minutes T8 after 10 hours ± 5 minutes
Within 120 minutes after T_0		Breakfast	
Between 60 minutes and 120 minutes after T_0		ABOUT-Product experience questionnaire	
Within 120 min after T_0		Collection and weighing of used P4M3 Gen 2.0 CA35 and CM35 Cartridges, collection of cigarette buttes	
After at least 4 hours after T_0		Lunch	
During nicotine washout		Nicotine washout	Optional: snacks and drinks
Ongoing		Support during period of abstinence from any	

Time	Blood Sample	Procedures	Additional Information
		tobacco and nicotine containing products	
Ongoing		AE/SAE, concomitant medication recording/ concomitant diseases status check	
Ongoing		Product events malfunctions/misuse	

Abbreviations: ABOUT = Assessment of behavioral outcomes related to tobacco and nicotine products; AE = Adverse event; ECG = Electrocardiogram; HPT = Human puffing topography; PK = Pharmacokinetic; SAE = Serious adverse event; VAS = Visual analogue scale

9.5 Day 3

The study activities performed on Day 3 prior to the time of discharge are listed in Table 10.

Table 10 Time Schedule – Discharge (Day 3)

Time	Blood Sample	Procedures	Additional Information
Prior to T_0		Weighing of P4M3 Gen 2.0 CA35 and CM35 Cartridge and connection of P4M3 Gen 2.0 to MDEDR HPT device	
Prior to T_0		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.
Within 15 minutes prior to T_0		VAS craving assessment	
5 minutes ± 1 minute prior to T_0	✓	Blood sampling for baseline nicotine level	Sample T14 after 24 hours ± 10 minutes from T_0 on Day 2
Just before T_0		Turning on P4M3 Gen 2.0 or lighting of cigarette	Performed by investigational site staff
Start of product use: T_0		P4M3 Gen 2.0 product use with MDEDR HPT recording Cigarette smoking without HPT recording	After approximately 24 hours of nicotine washout. Within ± 20 minutes of T_0 of prior study day.

Time	Blood Sample	Procedures	Additional Information
During/after 6 min *ad libitum* product use	✓	Blood sampling for nicotine PK	Post T_0, blood will be drawn at the following time points: T1 after 1 minute + 30 seconds T2 after 2 minutes + 1 minute T3 after 4 minutes + 1 minute T4 after 6 minutes + 1 minute T5 after 8 minutes + 1 minute T6 after 10 minutes + 1 minute T7 after 12 minutes + 1 minute T8 after 15 minutes ± 2 minutes T9 after 30 minutes ± 2 minutes T10 after 1 hour ± 5 minutes T11 after 2 hours ± 5 minutes T12 after 4 hours ± 5 minutes T13 after 10 hours ± 5 minutes
		VAS craving assessment, VAS liking assessment	Post T_0, assessments will be done at the following timepoints: T1 after 4 minutes ± 1 minute T2 after 10 minutes ± 1 minute T3 after 15 minutes ± 1 minute T4 after 30 minutes ± 2 minutes T5 after 1 hour ± 5 minutes T6 after 2 hours ± 5 minutes T7 after 4 hours ± 5 minutes T8 after 10 hours ± 5 minutes
Within 120 minutes after T_0		Breakfast	
Between 60 minutes and 120 minutes after T_0		ABOUT-Product experience questionnaire	
Within 120 min after T_0		Collection and weighing of used P4M3 Gen 2.0 CA35 and CM35 Cartridges, collection of cigarette buttes	

Time	Blood Sample	Procedures	Additional Information
Ongoing		Support during periods of abstinence from any tobacco and nicotine containing products	
	✓	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 10 hours of fasting.
		Urine analysis safety panel	
After at least 4 hours after T_0		Lunch	
		Urine pregnancy test (all female subjects)	
		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.
		AE/SAE, concomitant medication recording	
		Discharge	

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

9.6 Safety Follow-Up Period

After discharge at Day 3, the subjects will enter a 3-day Safety Follow-Up Period during which AE/SAEs reported by the subjects will be collected and the follow-up of AEs/SAEs will be conducted by the study investigational site as described in section 8.2.6.

9.7 Early Termination Procedures

When a subject is discontinued from the study, all early termination procedures listed in Table 11 are performed unless the subject refuses to perform the assessments or the procedures have already been performed during that study day.

Table 11 Early Termination

Blood Sample	Procedures	Additional Information
✓	Clinical laboratory parameters (hematology, clinical chemistry)	
	Urine analysis safety panel	
	Urine pregnancy test (all female subjects)	
	Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.
	ECG	After resting for at least 10 min in supine position prior to recording.
	Spirometry	After resting in sitting position for at least 15 minutes.
	Physical examination	
	Information on the risks of smoking/advice on smoking cessation and debriefing on P4M3 Gen 2.0	
	AE/SAE, concomitant medication recording	
	Product events malfunctions/misuse	If applicable
	Discharge	

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

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

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

Before the first subject is screened and included in the study, an Investigator meeting/site initiation visit will be conducted. During this meeting/visit, the general training of the study procedures and specific training on selected procedures will be performed and documented. All activities to be conducted will be described in the monitoring plan.

During the study, the Monitor will have regular contact with the investigational site, including routine monitoring visits. The frequency and purpose of the monitoring visits will be defined in the monitoring plan agreed with the Sponsor.

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

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.

The Monitor and the Sponsor's personnel will be available between visits, should the Investigator or other staff at the investigational site need information and/or advice.

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

10.2 Training of Staff

Prior to the screening of the first subject, an Investigator Meeting/Study Initiation Visit will be held. During this meeting/visit, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training to the relevant systems and other study-specific procedures. The activities of this meeting/visit will be described in the monitoring plan.

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

10.3 Audits and Inspections

Good Clinical Practice regulations require 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 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 was recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines and any applicable regulatory requirements. The Investigator or designee will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their investigational 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. By signing this protocol, the Investigator or designee 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 (DMP) and documents specified therein.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

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

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

11.1.2 Protocol Deviations

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

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

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

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

11.2 Data Handling

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

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

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

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

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

Additional details are covered in the DMP.

11.2.1 Data Verification

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

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

11.2.2 Coding

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

Adverse events, concomitant disease, medical/surgical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Prior/concomitant medication:	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 as defined in the DMP, the Sponsor organizes a data review and ensures that the resolution of all raised queries and quality control of the changed data are performed by the CRO before approving the database locked.

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

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

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Full details of the statistical analysis will be given in the Statistical Analysis Plan (SAP). The following statistical analyses will not be performed prior to the finalization of the SAP. Any changes to the planned statistical methods from the SAP will be documented in the clinical study report (CSR). The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Stratification Criteria

The sample enrollment will enforce at least 40% of each sex, therefore analyses will be stratified by sex, as well as unstratified, as detailed in the SAP.

12.1.2 Definitions for Statistical Data Analysis

For PK and PD analyses, baseline will be defined as the last assessment prior to T_0 (5 minutes prior to T_0) for each study day of exposure.

Nicotine PK parameters (e.g., T_{max}, C_{max}, $AUC_{0\text{-}Tmax}$) will be derived from background-corrected nicotine concentrations.

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by subject, study visit, product, and time point, unless otherwise specified.

Continuous 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, first and third quartiles, minimum and maximum.

For log normally distributed endpoints, geometric mean, geometric CV, and confidence interval will be presented additionally.

Nominal categorical variables will be summarized by frequency statistics (number and percentage), including the number of missing data as a category.

Ordinal categorical data (e.g., T_{max}) will be summarized by number of subjects (n), number and percent of subjects with missing data, median, first and third quartiles, and minimum and maximum.

For PK and PD endpoints, all analyses and summaries will be performed by product.

For safety endpoints, analyses and summaries will be performed by product and sequence, and overall.

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

For nicotine concentrations below the LLOQ (BLOQ):

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

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

12.1.5 Significance Level for Inferential Analysis

Not applicable.

12.2 Determination of Sample Size and Power Consideration

In this study 36 subjects will be randomized to 6 product use sequences. This sample size is empirically based as there are no considerations for statistical hypothesis.

In an analysis of confidence interval precision on the P4M3 Gen 2.0: cigarettes C_{max} ratios, performed with SAS with 10,000 simulations,

- The precision has been determined to be of 0.55, and
- The geometric coefficient of variation (GCV) has been determined to be of 50%.

12.2.1 Assumptions

The precision has been determined using the following geometric mean (GM), geometric coefficient of variation (GCV) and within subjects correlation assumptions for C_{max}:

- For all products the GCV is 80% (in previous study [5] GCV is in the range of 0.63 to 0.83)
- For usual brand of cigarettes, the GM is 12 ng/mL (in previous studies [32-34] this GM is in the range of 11 to 13)
- For P4M3 Gen 2.0 variants with 3.5% nicotine, the GM is 11 ng/mL (in previous a previous study [5] GM is in the range of 9.4 to 12)
- The correlation within subjects on log-transformed data is 0.8 (in previous studies [32-34] this correlation is in the range of 0.82 to 0.88)

12.2.2 Method

The analysis of confidence interval precision on the P4M3 Gen 2.0: cigarettes C_{max} ratios has been implemented using SAS, simulating 10000 sets of log-transformed data for 36 subjects with the assumptions described in section 12.2.1, the 3 periods and the 6 sequences of this cross-over design.

The statistical analysis has been performed with a linear model with repeated measurement including as fixed effect the sequence, the period, and the product exposure.

The P4M3 Gen 2.0:cigarettes C_{max} ratios and related confidence intervals have been determined by using the exponential of the difference between P4M3 Gen 2.0 variants and cigarettes on the log-transformed data.

Then precision has been determined as the 90^{th} percentile of the 95% confidence interval of the P4M3 Gen 2.0: cigarettes C_{max} ratios.

12.3 Analysis Populations

Populations will be described on the screened population.

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

Safety will be analyzed using the safety population.

12.3.1 Screened Population

The screened population consists of all subjects who underwent screening.

12.3.2 Safety Population

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

12.3.3 Randomized Population

The randomized population is a subset of the safety population and consists of all the subjects who were randomized at Admission (Day -1).

12.3.4 Pharmacokinetics Population

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

12.4 Demographics and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the PK population. This summary will also be performed for the randomized population if there is at least a difference of 1 subject between the populations.

Summaries will include sex, age, height, weight and BMI, nicotine/tobacco product use history, FTND, CYP2A6 activity and other endpoints that are only captured prior to product use.

These data will be summarized using the appropriate summary statistics as described in section 12.1.3.

12.5 Main Objective and Endpoints

12.5.1 Nicotine PK Parameter Analysis Variables

Nicotine PK parameters (section 3.1) will be derived from plasma nicotine concentration versus time data using a non-compartmental analysis (NCA) technique.

To minimize the carry-over effect in the nicotine plasma PK parameters (section 4.2), background-concentration correction will be applied to the concentration data. The baseline correction will be implemented by calculating the nicotine concentration parameters using adjusted concentration values as described below.

The nicotine terminal elimination rate constant λ_z (and terminal elimination half-life $t_{1/2z}$) will be estimated from the Day 2 PK samples (section 7.5.1) by using a linear regression on the log plasma nicotine concentration data. The regression analysis should contain data from at least 3 different time points in the terminal phase (including the last quantifiable concentration but C_{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: $C_t = uC_t - uC_0 * e^{-\lambda z \cdot t}$. Where, C_t is the corrected concentration at each time point, uC_t is the uncorrected concentration at each time point, uC_0 is the pre-use baseline concentration, λ_z is the Day 2 terminal elimination rate constant and t is the actual time [35]. For the purposes of background-correction of the plasma concentrations post-baseline the following formula will be applied: $C_t = uC_t - uC_0 * e^{-\lambda z \cdot t}$. Where, C_t is the corrected concentration at each time point, uC_t is the uncorrected concentration at each time point, uC_0 is the pre-use baseline concentration, λ_z is the Day 2 terminal elimination rate constant and t is the actual time [35].

The procedure of the baseline adjustment will be detailed in the SAP.

If plasma concentrations cannot be background-corrected in a sufficient number of subjects, alternative analysis methods will be used, as detailed in the SAP.

In particular, the following PK parameters will be derived from nicotine levels adjusted for baseline:

C_{max}	Maximum background-corrected plasma concentration. C_{max} will be reported as long as there is at least one quantifiable concentration post T_0.
T_{max}	Time to maximum background-corrected plasma nicotine concentration C_{max}.
$AUC_{0\text{-}2min}$	Area under the background-corrected plasma concentration-time curve from start of product use (T_0) to 2 minutes.
$AUC_{0\text{-}4min}$	Area under the background-corrected concentration-time curve from T_0 to 4 minutes.

$AUC_{0\text{-}Tmax}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to subject-specific time to maximum plasma concentration after T_0.
$AUC_{0\text{-}10h}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 10 hours.
$AUC_{0\text{-}last}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to the time of last quantifiable concentration.
$AUC_{0\text{-}infinity}$	Area under the background-corrected plasma nicotine concentration-time curve extrapolated from T_0 to infinity.
$_{max}(C_t/t)_{t\in]0,Tmax]}$	Maximum ratio of background-corrected concentration over time, from T_0 (excluded) to T_{max} (included)

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

12.5.2 Baseline Comparability

Not applicable.

12.5.3 Descriptive Summary

Endpoints will be summarized as described in section 12.1.3 using the randomized and the PK population.

12.5.4 Inferential Analysis

Additional details will be provided in the SAP.

12.5.4.1 Main Analysis

A mixed model analysis of variance (ANOVA) will be conducted on $AUC_{0\text{-}2min}$, $AUC_{0\text{-}4min}$, $AUC_{0\text{-}Tmax}$, $AUC_{0\text{-}10h}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}infinity}$, C_{max}, and $_{max}(C_t/t)_{t\in]0,Tmax]}$ endpoints in the natural logarithmic scale.

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

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

This approach is consistent with the guidelines in the European Medicines Agency's guidelines for bioequivalence investigations [36] and FDA's Center for Drug Evaluation and Research [37].

The analysis of T_{max} will be performed by conducting a Wilcoxon signed rank test and calculating the median T_{max} for each product along with the Hodges-Lehmann [32] estimate of the median difference between products, and the related 95% CI.

12.5.4.2 Sensitivity Analysis

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

12.6 Secondary Objectives and Endpoints

12.6.1 Pharmacodynamic (PD) Endpoints

PD endpoints are listed in section 3.2. More details on PD endpoints derivations will be provided in the SAP.

12.6.2 Human Puffing Topography Parameters

The following HPT Parameters will be measured per-puff on Day 1 to Day 3 using the MDEDR puffing topography device with P4M3 Gen 2.0:

Table 12 Human Puffing Topography Parameters for MDEDR Puffing Topography Device Per-Puff

Description	Variable	Unit
Puff number	Ni	
Puff volume	Vi	mL
Puff duration	Di	s
Average puff flow	Qmi	mL/s
Peak flow	Qci	mL/s
Inter puff interval	Ii	s
Sum of Ii and Di	DFi	s
Peak flow position	PosQci	%

The following HPT Parameters will be calculated per-product use experience from Day 1 to Day 3 using the MDEDR puffing topography device with P4M3 Gen 2.0 variants:

Table 13 Human Puffing Topography Parameters for MDEDR Puffing Topography Device Per-Product Use

Description	Variable	Formula	Unit
Total number of puffs	NPC	Σ Ni	
Total puff volume	TVOL	Σ Vi	mL
Average puff volume	AvgVi	Σ Vi / NPC, i=1 ... NPC	mL
Average puff duration	AvgDi	Σ Di / NPC, i=1 ... NPC	s
Total puff duration	TDi	Σ Di	s
Average flow	AvgQmi	Σ Qmi / NPC, i=1 … NPC	mL/s
Average peak flow	AvgQci	Σ Qci / NPC, i=1 … NPC	mL/s
Total inter puff interval	TIi	Σ Ii	s
Average inter puff interval	AvgIi	Σ Qci / NPC, i=1 … NPC	s
Total puffing duration	TDFi	Σ DFi	s
Puff Frequency	PFeq	NPC/(TDFi/60)	

12.6.3 Extent of Product Use

Endpoints related to amount of nicotine delivered from P4M3 Gen 2.0 and number of cigarettes are listed in section 3.2.

12.6.4 Descriptive Summary

Endpoints will be summarized as described in section 12.1.3 using the randomized and the PK population.

12.6.5 Inferential Analysis

Not applicable.

12.6.6 Safety Endpoints

In general, all safety data will be listed and tabulated using the approach described in section 12.1.3. Safety variables collected during exposure periods will also be reported by sequence.

AE data will serve for the assessment of safety. Other safety variables monitored in this study include: incidence of P4M3 Gen 2.0 product events including malfunction/misuse; vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; clinical chemistry, hematology, and urine analysis safety panel; physical examination; concomitant medication.

The number and percentage of subjects with AEs, SAEs, and product 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, AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events.

Safety laboratory assessments are performed on Day -1 and Day 3 in the morning prior to product use (Appendix A). Any lab related AEs on Day 3 will be assigned to the product used on the previous day.

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 period for ECG and vital signs and by Day for laboratory parameters, ECG and vital signs.

12.7 Exploratory Analyses

Exploratory analyses endpoints are listed in section 3.3.

12.7.1 Descriptive Summary

Endpoints will be summarized as described in section 12.1.3 using the randomized and the PK population.

12.7.2 Inferential Analysis

An analysis of covariance (ANCOVA) will be conducted by product use. The PK parameters will be transformed in the natural logarithmic scale. The model will include terms for sequence, period and product liking by the VAS-liking assessment. The results of this analysis will be presented by product in terms of:

- The percentage of variance explained by product liking by the VAS-liking assessment

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

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

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

13.1.1 Investigator

Investigator:	Melanie Fein, MD [redacted]

13.1.2 Sponsor

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

13.1.3 Other Responsibilities

Project Management:	[redacted]
Monitoring:	[redacted]
Data Management:	[redacted]
Pharmacokinetic Analyses:	[redacted]
Statistical Analyses:	[redacted]

	[redacted]

All duties and responsibilities transferred by the Sponsor to the above listed CROs will be defined in an agreement signed between the relevant two parties.

Any SAEs or pregnancies will be handled by the Investigator, study monitor (or Sponsor), as per the instructions listed in section 8.3.

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

13.2 Subject Recruitment

Subjects will be recruited from the volunteers' database maintained by the CRO. This database contains a pool of volunteers that are contacted whenever necessary to enroll subjects in a new study. Before the start of the new study, the Investigator and other relevant staff discuss with the volunteers' recruiter the study recruitment needs and specific requirements. On the basis of this information, the volunteers' recruiter queries the database, contacts potential volunteers to propose the study and evaluate their interest and availability. In addition to the volunteers database, new subjects often call or email the CRO asking to become a research volunteer, after hearing of the clinical site activities from other volunteers or friends or after checking the company web site. The CRO and its clinical site have detailed SOPs on the recruitment process.

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

Any documents that allow full identification of the subject (e.g., the subject's signed ICF) must be maintained in confidence by the 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.

13.4 Access to Source Documentation

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

The Investigator and all investigational 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).

13.5 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans and ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study and the actions taken will be maintained by the investigational site for the study, as required by ICH GCP [1] and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in section 8 of the ICH GCP Guideline [1].

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

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

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

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

- Signed informed consent documents for all subjects and master ICF.
- Subject identification code list, Screening log and Enrollment log (if applicable).
- Record of all communications between the Investigator and the IRB, composition of the IRB.
- Record of all communications/contact between the Investigator, the 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.
- 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., 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.
- 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.

13.6 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" [39]. 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.

13.7 Financial Disclosure

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

13.8 Publication and Disclosure Policy

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

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

13.9 Insurance

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

14 REFERENCE LIST

1. ICH E6 (R2), *Integrated addendum to ICH E6 (R1): guideline for good clinical practice - Current Step 4 version dated 9 November 2016.* 2016. **Available from: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf (Accessed on 17 January 2020)**.

2. World Medical Association (WMA), *Declaration of Helsinki - Ethical principles for medical research involving human subjects.* 2013. **Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (Accessed on 12 July 2018)**.

3. U.S. Department of Health and Human Services, *The health consequences of smoking - 50 years of progress: a report of the Surgeon General.* 2014.

4. WHO Study Group, et al., *WHO study group on tobacco product regulation - Report on the scientific basis of tobacco product regulations: fifth report of a WHO study group.* 2015.

5. Philip Morris Products S.A., *Unpublished on file data: Investigator's Brochure for Mesh 2.0. Edition 3*. 2020.

6. Robinson, R.J., et al., *Electronic cigarette topography in the natural environment.* PLoS One, 2015. **10**(6): p. e0129296.

7. Talih, S., et al., *Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions.* Nicotine Tob Res, 2015.

8. Farsalinos, K.E., et al., *Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naive users (smokers).* Sci Rep, 2015. **5**: p. 1-8.

9. Caldwell, B., W. Sumner, and J. Crane, *A systematic review of nicotine by inhalation: is there a role for the inhaled route?* Nicotine Tob Res, 2012. **14**(10): p. 1127-39.

10. Ebajemito, J.K., et al., *A randomised controlled single-centre open-label pharmacokinetic study to examine various approaches of nicotine delivery using electronic cigarettes.* Scientific reports, 2020. **10**(1): p. 1-10.

11. Helen, G.S., et al., *Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes.* Drug and alcohol dependence, 2017. **178**: p. 391-398.

12. Voos, N., et al., *Effect of e-cigarette flavors on nicotine delivery and puffing topography: results from a randomized clinical trial of daily smokers.* Psychopharmacology, 2020. **237**(2): p. 491-502.

13. Helen, G.S., et al., *Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes.* Addiction, 2015: p. 535-544.

14. Hukkanen, J., P. Jacob, 3rd, and N.L. Benowitz, *Metabolism and disposition kinetics of nicotine.* Pharmacol Rev, 2005. **57**(1): p. 79-115.

15. Marchand, M., et al., *Nicotine population pharmacokinetics in healthy adult smokers: a retrospective analysis.* Eur J Drug Metab Pharmacokinet, 2017.

16. Benowitz, N.L., et al., *Female sex and oral contraceptive use accelerate nicotine metabolism.* Clin Pharmacol Ther, 2006. **79**(5): p. 480-8.

17. Fagerström, K.O., *Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment.* Addict Behav, 1978. **3**(3-4): p. 235-41.

18. Heatherton, T.F., et al., *The Fagerström test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire.* Br J Addict, 1991. **86**(9): p. 1119-27.

19. Cappelleri, J.C., et al., *Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire.* Addictive Behaviors, 2007. **32**: p. 912–923.

20. FDA (Food and Drug Administration), *Food-effect bioavailability and fed bioequivalence studies.* 2002.

21. American Pharmacists Association, *Cytochrome P450 enzymes: substrates, inhibitors, and inducers*, in *Drug information handbook*. 2014. p. 2316-2324.

22. Raw, M., et al., *WHO Europe evidence based recommendations on the treatment of tobacco dependence.* Tob Control, 2002. **11**(1): p. 44-6.

23. Miller, M.R., et al., *Standardisation of spirometry.* Eur Respir J, 2005. **26**(2): p. 319-38.

24. Graham, B.L., et al., *Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement.* Am J Respir Crit Care Med, 2019. **200**(8): p. e70-e88.

25. Hu, G. and P.A. Cassano, *Antioxidant nutrients and pulmonary function: the Third National Health and Nutrition Examination Survey (NHANES III).* Am J Epidemiol, 2000. **151**(10): p. 975-81.

26. Fagerstrom, K., et al., *The Fagerstrom Test for Nicotine Dependence as a predictor of smoking abstinence: a pooled analysis of varenicline clinical trial data.* Nicotine and Tobacco Research, 2012. **14**(12): p. 1467-73.

27. Salzberger, T., et al., *Psychometric evaluation of the mCEQ applied to cigarettes and heat-notburn products in the US and Japan.* 2018. **Poster presented at the Society for Research on Nicotine and Tobacco Annual Meeting, Baltimore, MD, USA. Available from: https://www.pmiscience.com/library/publication/psychometric-evaluation-of-the-mceq-applied-to-cigarettes-and-heat-notburn-products-in-the-us-and-japan (Accessed on 16 April 2018)**.

28. Chrea, C., et al., *Assessing consumer responses to reduced risk products: experience at Philip Morris International in developing fit-for-purpose self-report instruments.* 2018. **Poster presented at the Fifth Global Forum on Nicotine, Warsaw, Poland. Available from: https://gfn.net.co/posters-2018/566-assessing-consumer-responses-to-reduced-risk-products-experience-at-philip-morris-international-in-developing-fit-for-purpose-self-report-instruments (Accessed on 20 August 2018)**.

29. Hatsukami, D.K., et al., *Subjective responses to oral tobacco products: scale validation.* Nicotine Tob Res, 2013. **15**(7): p. 1259-64.

30. Moyses, C., A. Hearn, and A. Redfern, *Evaluation of a novel nicotine inhaler device: part 2-effect on craving and smoking urges.* Nicotine Tob Res, 2015. **17**(1): p. 26-33.

31. FDA (Food and Drug Administration), *Guidance for industry - Assessment of abuse potential of drugs.* 2017.

32. Philip Morris Products S.A., *Nicotine pharmacokinetic profile and safety of the Tobacco Heating System 2.2 (THS 2.2)[ZRHR-PK-01-EU]*. **In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013-2014 [cited 2015 Jun 16]. Available from: http://clinicaltrials.gov/show/NCT01967732 NLM Identifier: NCT01967732**.

33. Brossard, P., et al., *Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers.* Regul Toxicol Pharmacol, 2017. **89**: p. 193-199.

34. Philip Morris Products S.A., *A single-center, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of THS 2.2 Menthol following single use in smokers compared to menthol conventional cigarettes and nicotine nasal spray [ZRHM-PK-06-US]*. **In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013-2014 [cited 2015 Jun 16]. Available from: http://clinicaltrials.gov/show/NCT01967719 NLM Identifier: NCT01967719**.

35. Kraiczi, H., A. Hansson, and R. Perfekt, *Single-dose pharmacokinetics of nicotine when given with a novel mouth spray for nicotine replacement therapy.* Nicotine Tob Res, 2011. **13**(12): p. 1176-82.

36. Committee for Medicinal Products for Human Use (CHMP) and European Medicines Agency (EMA), *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)*. 2010.

37. FDA (Food and Drug Administration), *Guidance for industry - Statistical approaches to establishing bioequivalence.* 2001. **Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf (Accessed on 24 April 2014)**.

38. Hodges, J.L. and E.L. Lehmann, *Estimation of location based on ranks tests.* Annals of Mathematical Statistics, 1963. **34**(2): p. 598-611.

39. ICH E3, *Structure and content of clinical study reports - Guideline.* 1995. **Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf (Accessed on 17 July 2014)**.

APPENDIX A SCHEDULE OF EVENTS

Study Day	Day -29 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3 Discharge	Day 4 to 6 Safety Follow-Up
Informed consent	●					
Information on the risks of smoking/advice on smoking cessation and debriefing on P4M3 Gen 2.0	●	●			● [q]	
Inclusion/exclusion criteria [a]	●	●				
P4M3 Gen 2.0 product demonstration	●					
Nicotine/Tobacco product use history	●	●				
Demographics [b], medical history, concomitant diseases	●	●[c]	●[c]	●[c]	●[c]	
Prior medication/ Concomitant medication [d]	●	●	●	●	● [q]	
Physical examination	●	●			● [q]	
Body height, weight and related BMI	●					
Vital signs [e]	●	●	●	●	● [q]	
ECG [f]	●	●			● [q]	
Spirometry	●	●			● [q]	

Study Day	Day -29 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3 Discharge	Day 4 to 6 Safety Follow-Up
Blood and urine sample for hematology, clinical chemistry, urine analysis safety panel [g]	•	•			• [q]	
Blood sample for serology [h]	•					
Urine sample for drug test	•	•				
Urine sample for cotinine test	•	•				
Urine pregnancy test (females)	•	•			• [q]	
Alcohol breath test	•	•				
Blood sample for *trans*-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma [i]		•				
Fagerström Test for Nicotine Dependence	•					
P4M3 Gen 2.0 product test [j]		•				
Enrollment		•				
Randomization		•				
6 min *ad libitum* use			•	•	•	
Human puffing topography [k]			•	•	•	
Blood sample collection for plasma nicotine [l]			•	•	•	
ABOUT-Product experience questionnaire [m]			•	•	•	

Study Day	Day -29 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3 Discharge	Day 4 to 6 Safety Follow-Up
VAS craving assessment [n]			●	●	●	
VAS liking assessment [n]			●	●	●	
AE/SAE recording [o]	●	●	●	●	● [q]	●
Product events, Malfunctions and Misuse		●	●	●	● [q]	
Support during periods of abstinence from any tobacco and nicotine containing products (as required)		●	●	●	●	
Collection of used products			●	●	●	
Weight of P4M3 Gen 2.0 Cartridge [p]			●	●	●	

Abbreviations: ABOUT = Assessment of Behavioral OUtcomes related to Tobacco and nicotine products; AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; SAE = Serious adverse event;

a. Prior to enrollment at Admission on Day -1, the following inclusion and exclusion criteria will be re-checked: Inclusion Criteria: (4) Subject has smoked ≥ 10 commercially available cigarettes per day for 4 weeks prior to Screening Visit and Admission. Smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL), (5) Subject does not plan to quit smoking or using other nicotine/tobacco-containing products in the next 3 months (7) Subject is available during the study period and willing to comply with study procedures, including periods of abstinence from any nicotine/tobacco containing products. Exclusion criteria: (10) Subject has a positive urine drug test, (15) For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding, (16) For women of childbearing potential only: subject does not agree to use an acceptable method of effective contraception, (17) Use of estrogen-containing hormonal contraception or hormone replacement therapy.
   The following eligibility criteria will only be checked at Admission: (7) Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission, whichever is longer, which has an impact on CYP2A6 activity.

b. Sex, date of birth/age, race and ethnicity.

c. Concomitant disease status.

d. All medication taken within 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 Day -1 is an exclusion criterion.

e. Systolic and diastolic blood pressure, pulse rate and respiratory rate. On Day 1 to Day 3, vital signs will be assessed prior to T_0.

f. At Screening an ECG will be performed after signed ICF and at least 1 hour after smoking cigarettes, on Day -1 an ECG will be performed prior to enrollment, on Day 3 an ECG will be performed 60 minutes ± 10 minutes after T_0.

g. Blood samples should be taken in the morning of the Screening visit, Admission (Day -1) and Discharge (Day 3) or at Early termination. Subjects should have fasted for at least 10 hours prior to safety laboratory assessments except at the Screening visit and Early termination where non-fasting samples will be used.

h. Tests for hepatitis B (HbsAg), hepatitis C (HCV antibody) virus and human immunodeficiency virus (anti-HIV1/2) will be performed at the Screening Visit.

i. Sample taken prior to P4M3 Gen 2.0 product test.

j. On Day -1, after enrollment, subjects will perform a product test using P4M3 Gen 2.0 Classic Auburn 3.5% variant (CA35) *ad libitum* for up to 10 minutes.

k. On Day 1 to Day 3, subjects will smoke a single cigarette or will use one P4M3 Gen 2.0 with CA35 and CM35 variant *ad libitum* for 6 minutes (±30 seconds) according to the randomized product use sequence. P4M3 Gen 2.0 use with the MDEDR puffing topography device connected with data recording for 6 minutes (±30 seconds).

l. On Day 1, 15 blood samples will be taken for determination of nicotine concentration: one blood sample will be taken prior to the start of product use (T_0) 5 minutes ± 1 minute (T-1). Thereafter in relation to T_0, blood will be drawn at the following time points: T1 after 1 minute + 30 seconds, T2 after 2 minutes + 1 minute, T3 after 4 minutes + 1 minute, T4 after 6 minutes + 1 minute, T5 after 8 minutes + 1 minute, T6 after 10 minutes + 1 minutes, T7 after 12 minutes + 1 minute, T8 after 15 minutes ± 2 minutes, T9 after 30 minutes ± 2 minutes, T10 after 1 hour ± 5 minute, T11 after 2 hours ± 5 minutes, T12 after 4 hours ± 5 minutes, T13 after 10 hours ± 5 minutes and T14 after 24 hours ± 10 minutes (Day 1 and Day 2 only). The sample T14 on Day 1 will also be used to determine the nicotine baseline concentration prior to T_0 on Day 2.
On Day 2, 14 blood samples will be collected for determination of nicotine PK after allocated product use at the same time points, except timepoint T-1. The sample T14 after T_0 on Day 1 will also be used to determine the nicotine baseline concentration prior to T_0 on Day 2 and similarly, T14 after T_0 on Day 2 for nicotine baseline concentration prior to T_0 on Day 3.
On Day 3, 13 blood samples will be collected for determination of nicotine PK after allocated product use. The sample T14 after T0 on Day 3 will not be.
On Day 2 and 3, 4 blood samples will be taken for determination of the terminal elimination half-life ($t_{1/2z}$). Blood samples will be taken in relation to T_0 from Day 2 at the following time points: T1z after 8 hours ± 5 minutes, T2z after 12 hours ± 5 minutes, T3z after 16 hours ± 10 minutes and T4z after 20 hours ± 10 minutes.

m. On Day 1 to Day 3, the ABOUT-Product experience questionnaire will be answered within 60 to 120 minutes after T_0.

n. On Day 1 to Day 3, VAS craving and VAS liking assessment at: Within 15 minutes prior to T_0 (VAS craving only), after T_0 for VAS craving and VAS liking assessments at 4 minutes ± 1 minute, 10 minutes ± 1 minute, 15 minutes ± 1 minute, 30 minutes ± 2 minutes, 1 hour ± 5 minutes, 2 hours ± 5 minutes, 4 hours ± 5 minutes, 10 hours ± 5 minutes.

o. Spontaneous reporting of new AEs/SAEs by the subject and active follow-up of ongoing AEs/SAEs by the site.

p. On Day 1 to Day 3, P4M3 Gen 2.0 Cartridges will be weighed before T_0. P4M3 Gen 2.0 Cartridges will be weighed within 120 min after T_0.

q. Early termination assessments to be conducted in subjects who withdraw consent / are discontinued from the study.

APPENDIX B PARTICIPATING LABORATORIES

Bioanalytical laboratory (Plasma Nicotine and CYP2A6 analyses):

[redacted]

Safety Laboratory:

[redacted]

APPENDIX C ABNORMAL LABORATORY VALUES GRADING

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)	<LLN - 130	125-129 mmol/L and asymptomatic	125-129 symptomatic; 120-124 regardless of symptoms	<120
Sodium – Hypernatremia (mmol/L)	>ULN - 150	>150 - 155 intervention initiated	>155 - 160; hospitalization indicated	>160
Potassium – Hyperkalemia (mmol/L)	>ULN - 5.5	>5.5 - 6.0 intervention initiated	>6.0 -7.0; hospitalization indicated	>7.0
Potassium – Hypokalemia (mmol/L)	<LLN - 3.0	<LLN - 3.0; symptomatic; intervention indicated	<3.0 - 2.5; hospitalization indicated	<2.5
Glucose – Hypoglycemia (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:	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences ; urgent intervention indicated
Creatinine increased	>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 (g/dL) (g/L)	<LLN – 3; <LLN - 30	<3 – 2; <30 - 20	<2; <20	Life-threatening consequences

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Alkaline phosphatase increased	>ULN - 2.5 x ULN if >	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
ALT / AST increased	>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	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Lactate dehydrogenase (LDH) increased	>ULN	-	-	-
Blood bilirubin increased (total and direct)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Cholesterol high (mg/dL) (mmol/L)	 >ULN - 300; >ULN - 7.75	 >300-400; >7.75-10.34	 >400-500; >10.34-12.92	>500; >12.92
Triglycerides - Hypertriglyceridemia (mg/dL) (mmol/L)	 150 – 300; 1.71 – 3.42	 >300 – 500; >3.42 – 5.70	 >500 – 1000; >5.70 – 11.40	>1000; >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:

[a] Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.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) (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 – (g/dL)	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-
WBC Decrease – (cell/mm3) (109/L)	 <LLN – 3000; <LLN – 3.0	 <3000 - 2000; <3.0 – 2.0	 <2000 - 1000; <2.0 – 1.0	 <1000; <1.0
Lymphocytes increase (cell/mm3)	 -	 >4,000 – 20,000	 >20,000	 -
Lymphocytes decrease (cell/mm3) (109/L)	 <LLN – 800; <LLN – 0.8	 <800 - 500; <0.8 – 0.5	 <500 - 200; <0.5 – 0.2	 <200; <0.2
Neutrophils Decrease (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 (cell/mm^3) (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:

[a] Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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)
Glucose	Present	-	-	-
Red blood cell traces (Hematuria)	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental Activities of Daily Living	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care Activities of Daily Living	Life-threatening consequences; urgent invasive intervention indicated
Protein	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs;	4+ proteinuria; ≥3.5 g/24 hrs;	

Data Source:

[b] Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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 D HUMAN PUFFING TOPOGRAPHY PARAMETERS

Per-Puff Parameters

Description	Variable	Unit
Puff number	Ni	
Puff volume	Vi	mL
Puff duration	Di	s
Average puff flow	Qmi	mL/s
Peak flow	Qci	mL/s
Inter puff interval	Ii	s
Sum of Ii and Di	DFi	s
Peak flow position	PosQci	%

Per-Product use experience Parameters

Description	Variable	Formula	Unit
Total number of puffs	NPC	Σ Ni	
Total puff volume	TVOL	Σ Vi	mL
Average puff volume	AvgVi	Σ Vi / NPC, i=1 ... NPC	mL
Average puff duration	AvgDi	Σ Di / NPC, i=1 ... NPC	s
Total puff duration	TDi	Σ Di	s
Average flow	AvgQmi	Σ Qmi / NPC, i=1 … NPC	mL/s
Average peak flow	AvgQci	Σ Qci / NPC, i=1 … NPC	mL/s
Total inter puff interval	TIi	Σ Ii	s
Average inter puff interval	AvgIi	Σ Qci / NPC, i=1 … NPC	s
Total puffing duration	TDFi	Σ DFi	s
Puff Frequency	PFeq	NPC/(TDFi/60)	

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