PMI RESEARCH & DEVELOPMENT

Clinical Study Protocol

P3P-PK-01-CH

Study Title:	A single-center, open-label, randomized, crossover study to investigate the nicotine pharmacokinetic profile, pharmacodynamics, safety and tolerability of four P3P variants in smoking healthy adult subjects
Short Name:	Nicotine pharmacokinetics and pharmacodynamics, safety and tolerability of P3P
Registration Number:	Not assigned
Product Name:	P3P
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version Number:	1.0
Date:	24 July 2017
Authors:	[redacted], PhD, Clinical Scientist [redacted], MSc, Study Statistician [redacted], MD, Medical Safety Officer

SYNOPSIS

Sponsor:

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

Product Name:

P3P

Study Title:

A single-center, open-label, randomized, crossover study to investigate the nicotine pharmacokinetic profile, pharmacodynamics, safety and tolerability of four P3P variants in smoking healthy adult subjects

Study Number:

P3P-PK-01-CH

Short Study Title:

Nicotine pharmacokinetics and pharmacodynamics, safety and tolerability of P3P

Objectives and Endpoints:

The goal of the proposed research study is to evaluate the pharmacokinetic profiles of four P3P variants (differing in nicotine powder particle size, nicotine concentration and in the absence or presence of a flavoring system), following a fixed puffing regimen and an *ad libitum* use period. In addition, pharmacodynamic effects (subjective effects and related behavioral assessments), as well as human puffing topography will be evaluated, to provide further insights on product acceptance and product use. Safety will also be assessed throughout the study.

Primary Objective and Endpoints:

1. To evaluate the plasma concentration-time profile of nicotine and the derived PK parameters (with and without adjustment for baseline nicotine concentrations) of four P3P variants from the fixed puffing regimen.

   Endpoints:

   - Plasma nicotine concentration-time profile
   - Maximum plasma concentration [C_{max}]

- Time to the maximum concentration [t_{max}]
- Area under the concentration-time curve from start of product use ($T_{0\ fix}$) to 4 hours [$AUC_{fix\ (0\text{-}4h)}$]

Secondary Objectives and Endpoints:

1. To evaluate the plasma concentration-time profile of nicotine and the derived PK parameters (with and without adjustment for baseline nicotine concentrations) of four P3P variants from the *ad libitum* use period.

   Endpoints:

   - Plasma nicotine concentration-time profile
   - Peak plasma nicotine concentration [C_{peak}]
   - Time to peak plasma nicotine concentration [t_{peak}]
   - Trough plasma nicotine concentration [C_{trough}]
   - Average of plasma nicotine concentration from $T_{0\ ad\ lib}$ to 1 hour [$C_{average}$]
   - Area under the concentration-time curve from start of product use ($T_{0\ ad\ lib}$) to 4 hours [$AUC_{ad\ lib\ (0\text{-}4h)}$]

2. To evaluate the pharmacodynamic effects (subjective effects and related behavioral assessments) of four P3P variants.

   Endpoints:

   - Visual Analogue Scale (VAS)-craving assessment from the fixed puffing regimen and *ad libitum* use period
   - Product evaluation by an adapted version of the modified Cigarette Evaluation Questionnaire (adapted mCEQ) following the *ad libitum* use period
   - Sensory Questionnaire (SQ) following the *ad libitum* use period

3. To evaluate human puffing topography (HPT) of four P3P variants during the fixed puffing regimen and the *ad libitum* use period.

   Endpoints:

   - Per-puff parameters and per-product use experience parameters

4. To estimate the amount of powder aerosolized from P3P from the fixed puffing regimen and the *ad libitum* use period.

   Endpoints:

   - Weight difference of P3P before and after use

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

   Endpoints:

   - Incidence of adverse events (AEs), serious adverse events (SAEs)
   - Frequency of AEs, SAEs
   - Incidence of P3P product events including malfunction/misuse
   - Frequency of P3P product events including malfunction/misuse
   - Physical examination changes from baseline
   - Cough changes from baseline (Visual Analogue Scale and three Likert scales)
   - Electrocardiogram (ECG) changes from baseline (heart rate; PR, QRS, QT intervals, and QT interval corrected according to Bazett's [QTcB] and Fridericia's [QTcF] formula)
   - Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
   - Spirometry changes from baseline (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEV_1/FVC)
   - Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel
   - Concomitant medications

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

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

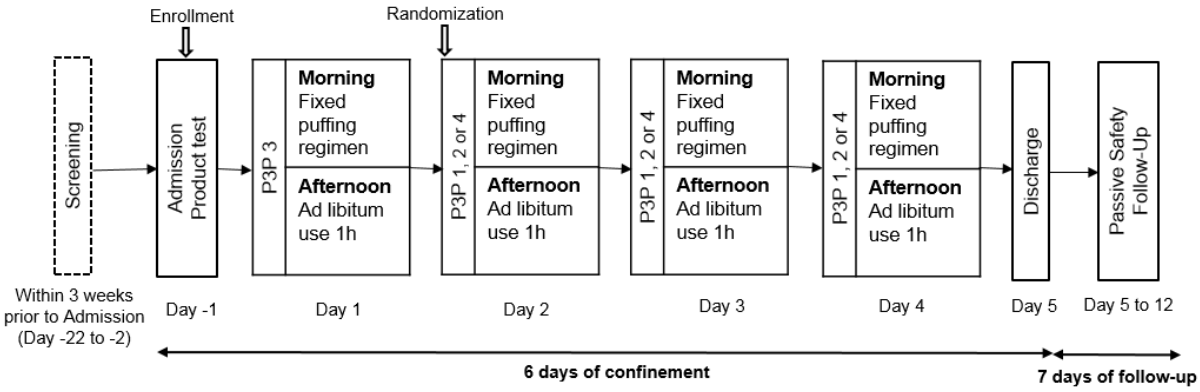
Study Hypothesis:

There are no statistical hypotheses to be tested.

Study Design:

This is a single-center, open-label, randomized, crossover study to evaluate the pharmacokinetic profiles of four P3P variants (differing in nicotine powder particle size, nicotine concentration and in the absence or presence of a flavoring system), following a fixed puffing regimen and an *ad libitum* use period. In addition, pharmacodynamic effects (subjective effects and related behavioral assessments), as well as human puffing topography, will be evaluated, to provide further insights on product acceptance and product use. Safety will also be assessed throughout the study.

A Screening Visit will be conducted within 3 weeks prior to Admission to the investigational site (see Figure 1). A demonstration of P3P, without product use, will be done by the investigational site staff during the Screening Visit.



P3P 1 characteristics: 2 mg nicotine; 2.25 µm nicotine powder particle size; unflavored
P3P 2 characteristics: 2 mg nicotine; 2.25 µm nicotine powder particle size; flavored
P3P 3 characteristics: 1 mg nicotine; 2.25 µm nicotine powder particle size; flavored
P3P 4 characteristics: 2 mg nicotine; 1.8 µm nicotine powder particle size; flavored

Figure 1 Study Flow Chart

Subjects will return to the investigational site for Admission (Day -1). Subjects should have been fasting for at least 6 hours prior to Admission. After confirmation of eligibility, subjects will be enrolled. All subjects that are not enrolled will be considered as screen failures. At Admission, enrolled subjects will perform a product test using up to three P3P 3 products. After the product test, subjects not willing and/or unable to use P3P will be discontinued from the study. Subjects willing to continue their participation in the study after product test will start their confinement phase.

On Day 1, after at least 10 hour abstinence from any tobacco/nicotine containing products, subjects will use P3P 3 during a fixed puffing regimen comprising of 12 puffs in total at a rate of one inhalation every 30 seconds (± 5 seconds) in the morning and during an *ad libitum* use period for 60 minutes (± 5 minutes) in the afternoon. The start of product use for fixed puffing

and for the *ad libitum* use period will be defined as $T_{0\ fix}$ and $T_{0\ ad\ lib}$, respectively. There will be a washout period of at least 10 hours between $T_{0\ fix}$ and $T_{0\ ad\ lib}$.

A total of 10 blood samples will be taken for fixed puffing PK parameter estimation. One blood sample will be taken 15 minutes ± 5 minutes (T-1) prior to $T_{0\ fix}$. Thereafter in relation to $T_{0\ fix}$, blood will be drawn at the following time points: T1 after 2 minutes ± 1 minute, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, and T9 after 4 hours ± 5 minutes.

A total of 8 blood samples will be taken for the *ad libitum* PK parameter estimation. One blood sample will be taken 15 minutes ± 5 minutes (T-1) prior to $T_{0\ ad\ lib}$. In relation to $T_{0\ ad\ lib}$, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes and T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, and T7 after 4 hours ± 5 minutes.

Pharmacodynamic effects related to craving will be assessed using a VAS scale at different timepoints. For the fixed puffing regimen the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ fix}$, all other assessments will be done after $T_{0\ fix}$, at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. For the *ad libitum* use period the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ ad\ lib}$, all other assessments will be done after $T_{0\ ad\ lib}$, at 10 minutes ± 2 minutes, at 20 minutes ± 2 minutes, 30 minutes ± 5 minutes, 40 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. VAS will be assessed immediately after the collection of the time-matching PK samples.

Product evaluation and sensory questionnaires will be assessed after the end of the *ad libitum* use period.

A puffing topography device will be attached to each P3P during both the fixed puffing regimen and the *ad libitum* use period. There will be one recording of HPT parameters per product use. Each P3P will be weighed before and after product use to estimate the amount of nicotine delivered in the aerosol. The number of P3P used during the *ad libitum* use period will be recorded.

In the morning of Day 2, after confirmation that there are no safety concerns for each subject to continue in the study based on the Investigator's judgement, 18 subjects will be randomized to one of the following six sequences of the remaining P3P variants in order to cross-over the use of P3P 1, P3P 2 and P3P 4 following a 2 Latin squares design balanced for first order carryover effects among the 3 variants.

Sequence	Day 2	Day 3	Day 4
1	P3P 2	P3P 4	P3P 1
2	P3P 4	P3P 1	P3P 2
3	P3P 1	P3P 2	P3P 4

4	P3P 1	P3P 4	P3P 2
5	P3P 2	P3P 1	P3P 4
6	P3P 4	P3P 2	P3P 1

Subjects discontinued before randomization will be replaced to reach 18 randomized subjects.

Subjects discontinued after randomization will not be replaced.

If a sufficient number of subjects are already randomized to the study sequences, any supernumerous subjects will be discontinued from the study prior to randomization only.

On Days 2, 3 and 4, subjects will be instructed to use the assigned P3P variant for the given study day for a fixed puffing regimen in the morning and an *ad libitum* use period in the afternoon as described for Day 1. At each study day including Day 1, start of product use should be at approximately the same time for fixed puffing in the morning and for *ad libitum* use in the afternoon with at least 10 hour washout period between $T_{0\ fix}$ and $T_{0\ ad\ lib}$. There will be a washout of at least 10 hours following $T_{0\ ad\ lib}$ with respect to the $T_{0\ fix}$ of the morning of the following study day to allow adequate background correction of the nicotine plasma concentrations. The assessments performed at Days 2, 3 and 4 will be the same as those described for Day 1.

On Day 5, there will be no product use but subjects will remain at the investigational site for additional PK blood sampling for the purposes of estimating the terminal elimination half-life. A total of 5 blood samples will be taken in relation to $T_{0\ ad\ lib}$ from the last product use at the following time points: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes, T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes and T5 after 24 hours ± 30 minutes.

During confinement, the use of any tobacco and nicotine containing products, apart from P3P use assigned on the assessment days, will not be allowed. Use of tobacco and nicotine containing products will not be restricted after Discharge on Day 5.

After Discharge on Day 5 or early termination date, the subjects will enter a 7-day Safety Follow-Up Period during which new AE/SAEs spontaneously reported by the subjects will be collected.

Any non-serious AE that is ongoing at the time of Discharge or early termination will be followed-up by the Investigator or designee 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) or lost to follow up. At the end of the Safety Follow-Up Period, all ongoing non-serious AEs will be documented as "ongoing" and no follow-up information will be sought for them anymore by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly.

All SAEs will be followed up by the Investigator or designee, despite their continuation after the end of the 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).

SAE reported after the end of the study and considered related to the investigational product by the Investigator must be captured and reported to UBC/PMI regardless of time after end of the study.

All subjects discontinued from the study at any time after enrollment, will enter the 7 day Safety Follow-Up Period.

Study Population and Eligibility Criteria:

Subjects must meet all of the following inclusion criteria to 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 21 and 65 years old.
3. Subject is White.[a]
4. Subject has been a smoker for at least the last 3 years prior to the Screening Visit.
5. Has smoked ≥ 10 commercially available cigarettes per day for the last 4 weeks prior to Screening Visit. Smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).
6. Subject does not plan to quit smoking within 2 months after Screening Visit.
7. 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).
8. Availability for the entire study period and willingness to comply with study procedures, including smoking interruptions.
9. Ready to accept using the P3P product.

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 and/or 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 clinically significant medical condition (including safety laboratory), 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 3 months prior to Screening Visit.
6. Subject has a BMI < 18.5 kg/m^2 or > 32.0 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 positive alcohol breath test and/or a history of alcohol abuse that could interfere with the subject's participation in study.
10. Subject has a positive urine drug test.
11. Subject or one of their family members[b] is a current or former employee in the tobacco industry.
12. Subject or one of their family members[b] is an employee of the investigational site or of any other parties involved in the study.
13. Subject has participated in another clinical study within 3 months prior to the Screening Visit. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study.
14. Subject has been previously screened or enrolled in this study.
15. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission Visit) or is breastfeeding.
16. For women of childbearing potential only [c]: subject does not agree to use an acceptable method of effective contraception.[d]
17. Use of estrogen-containing hormonal contraception or hormone replacement therapy.

[a] As defined by FDA guidance on Collection of Race and Ethnicity Data in Clinical Trials(1)

[b] 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"

[c] Women who are not of childbearing potential meet at least one of the following criteria:
Have undergone hysterectomy or bilateral tubal ligation,
Have medically confirmed ovarian failure, 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).

[d] Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, vasectomized partner(s), from Screening until the end of the Safety Follow-up Period. Hormonal contraception with estrogen containing products is NOT allowed in this study.

Investigational Products

P3P generates an inhalable aerosol from nicotine powder when air is drawn through it. P3P is a single use product that has a body in the form of a tube, similar to a cigarette, and contains a capsule. The capsule is pierced (activated) using a P3P piercing accessory before use. The P3P capsule contains the nicotine powder composed of either solely nicotine salt or nicotine salt blended with mentholated flavor powder in a 4:1 ratio. The nicotine powder is generated by spray-drying nicotine, [redacted] and [redacted] The nicotine powder has a median particle size of 1.8 ± 0.2 µm or 2.25 ± 0.2 µm allowing deep lung deposition whereas the flavor particles have a particle size > 50 µm and deposit in the oropharyngeal cavity. A single P3P product contains 1 or 2 mg of nicotine, depending on the P3P variant.

The following P3P variants will be tested in this study and they differ in nicotine powder particle size, nicotine concentration, and in the absence or presence of a flavoring system:

P3P variant	Nicotine content	Nicotine powder particle size	Total amount of nicotine/ product	Contains flavor particles
P3P 1	5%	2.25 ± 0.2 µm	2 mg	no
P3P 2	5%	2.25 ± 0.2 µm	2 mg	yes
P3P 3	2.5%	2.25 ± 0.2 µm	1 mg	yes
P3P 4	5%	1.8 ± 0.2 µm	2 mg	yes

Study Duration:

The entire study per subject will last 14 to 34 days. This will include a Screening period of up to 3 weeks prior to Admission (Day -22 to Day -2), 6 days of confinement (Day -1 to time of Discharge on Day 5), and a 7-day passive Safety Follow-Up Period (from time of Discharge at Day 5 until Day 12). The end of the study (EOS) for a subject is defined as either the Discharge on Day 5, or the date of early termination of the subject, plus the 7 days for the passive Safety Follow-Up Period. The end of the whole study corresponds to the individual EOS of the last subject.

Statistical Methods:

All endpoints will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data, arithmetic means and standard deviations (mean and SD), median, first and third quartiles, minimum and maximum; for log normally distributed endpoints geometric mean, geometric coefficient of variation (CV) will be presented instead of arithmetic mean and SD. 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.

The PK population is the primary analysis set for all PK, PD, and HPT endpoints. The PK population is composed of all subjects who gave informed consent, completed at least one of

the single use of P3P, for whom at least one primary PK parameter could be derived and with no major protocol deviation impacting evaluability. In particular, non-safety endpoints will be analyzed as follows:

PK: Nicotine PK parameters will be derived from plasma nicotine concentration versus time data using non-compartmental analysis (NCA). For both the fixed puffing regimen and the *ad libitum* use period, PK parameters will be derived and reported with and without baseline nicotine concentration adjustment.

PK parameters will be summarized by P3P variant and analyzed logarithmically transformed using a mixed model with fixed terms for sequence, study day, product variant, and using subject nested within sequence as random effect.

PD: PD will be summarized as follows:

- VAS craving assessments will be summarized over time by P3P variant and by product use regimen. The scores will be assessed using a mixed model with sequence, study day, product variant, baseline value prior to product use, and the interaction of product variant and time point as fixed effects and subjects nested within sequence as random effect including the assessment time points as repeated measurements. Additionally, the VAS craving score will be analyzed as AUC_{VAS} for each puffing regimen: $AUC_{VAS\ fix\ (0\text{-}4h)}$ and $AUC_{VAS\ ad\ lib\ (0\text{-}4h)}$ (similar to the calculation of nicotine plasma $AUC_{VAS\ (0\text{-}4h)}$, averaged over the total time of VAS collection period) and analyzed using the same model as for the PK parameters , with PD parameters analyzed in the regular scale.
- Adapted mCEQ subscale scores and SQ answers will be summarized with descriptive statistics and displayed graphically by P3P variant. The scores/answers will be analyzed using a mixed model with fixed terms for sequence, study day, product variant, and using subject nested within sequence as a random effect.

Least squares mean differences (ratios for log-normal data) will be presented for the analysis of PK and PD endpoints, together with 95% confidence interval for the following effects of interest:

- P3P 2 vs P3P 3, to describe the effect of an increase of nicotine powder concentration from 2.5% to 5%
- P3P 2 vs P3P 4, to describe the effect of a decrease from 2.25 to 1.8 µm of the median particle size of the nicotine powder
- P3P 2 vs P3P 1, to describe the effect of flavor

HPT parameters will be summarized by P3P variant and by product use regimen.

Safety analysis: The safety population will comprise all enrolled subjects who are exposed to P3P during the study. AE records will serve for the primary assessment of safety data. All safety data will be listed and AEs will be summarized by product variant (fixed puffing

regimen and *ad libitum* use periods will be combined at the product variant level). Safety measurements assessed both after fixed puffing regimen and *ad libitum* use (vital signs, ECG etc.) will be summarized per fixed puffing/*ad libitum* use regimen and product variant.

Sample Size:

The sample size is empirically based, as there is no prior information on which to base it, and as there are no considerations for statistical hypothesis.

As per study design P3P 3 is the first product variant used by all subjects at Day 1 for safety reasons (i.e P3P 3 has the lowest nicotine concentration of all P3P variants). As a result, only the 3 remaining product variants will be randomized over Day 2-4, which leads to 6 possible sequences. Considering that this study is a pilot investigation, and that we are expecting a low drop-out rate, 3 subjects will be allocated to each sequence. Therefore, 18 subjects will be randomized.

A sufficient number of eligible subjects will be enrolled and exposed to P3P 3 at Admission (Day -1) and Day 1 to ensure randomization of 18 subjects to one of six possible sequences at Day 2. At least 8 subjects of each sex will be randomized to ensure each sex represents at least 40% of the randomized population.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

Adapted mCEQ	Adapted version of the modified cigarette evaluation questionnaire
AE	Adverse event
$AUC_{ad\ lib\ (0\text{-}4h)}$	Area under the concentration-time curve from $T_{0\ ad\ lib}$ to 4h after $T_{0\ ad\ lib}$
$AUC_{fix\ (0\text{-}4h)}$	Area under the concentration-time curve from $T_{0\ fix}$ to 4h after $T_{0\ fix}$
BMI	Body mass index
$C_{average}$	Average plasma nicotine concentration during *ad libitum* use period
C_{max}	Maximum concentration
C_{peak}	Highest plasma nicotine concentration during *ad libitum* use period
C_{trough}	Trough plasma nicotine concentration during *ad libitum* use period
CDISC	Clinical data interchange standards consortium
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	Coefficient of variation
CYP2A6	Cytochrome P450 2A6
DCF	Data clarification form
DMP	Data management plan
DVP	Data validation plan
ECG	Electrocardiogram
EOS	End of study
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good clinical practice
GMP	Good manufacturing 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
IEC	Independent ethics committee
IP	Investigational product
LLOQ	Lower limit of quantification
λ_z	Terminal elimination rate constant
MedDRA	Medical dictionary for regulatory activities
NCA	Non-compartmental analysis
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PMI	Philip Morris International
RRP	Reduced risk product
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SHM	Sample handling manual
SMF	Study master file
SMP	Safety management plan
SOP	Standard operating procedure
SQ	Sensory questionnaire
$T_{0\ ad\ lib}$	Time point of start of first product use at the *ad libitum* use period
$T_{0\ fix}$	Time point of start of product use at the fixed puffing regimen
$t_{1/2z}$	Terminal elimination half-life
t_{max}	Time to maximum concentration
t_{peak}	Time to peak plasma nicotine concentration at the *ad libitum* use period
UBC	United BioSource Corporation
ULOQ	Upper limit of quantification
VAS	Visual analogue scale
WHO	World health organisation

Definitions of Terms

End of Study	The end of the study (EOS) for a subject is defined as either the Discharge at Day 5, or the date of early termination of the subject, plus the 7 days for the Safety Follow-up Period. The end of the whole study corresponds to the individual EOS of the last subject.
Enrollment	On Admission Visit for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily assessed and met.
Randomization	Assignment to the respective sequence of product use at Day 2.
Screen failure	Subject who signs the ICF but is not enrolled at Admission.

1 ETHICS AND REGULATIONS

1.1 Ethics Committee 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 including questionnaires and instructions to be provided to the subjects, Investigator's brochure [IB], available safety information, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the Independent Ethics Committee [IEC]), will be submitted for review and approval to the relevant IEC. The IEC shall be appropriately constituted and perform its functions in accordance with the International Conference on Harmonization (ICH) Tripartite Guidance for Good Clinical Practice (GCP) (2) and local requirements, as applicable.

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

The written approval from the IEC will be filed in the Investigator file, and a copy will be filed in the study master file (SMF) at the Sponsor or designated organization. No assessment can be performed on the subjects before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC.

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

These requirements for approval should in no way prevent any action from being taken by the Investigator or designee 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 or designee, and is implemented for safety reasons, the Sponsor and the IEC should be informed immediately. The Investigator is responsible for local reporting (e.g., to the IEC) of SAEs that occur during the study, according to local regulations.

Relevant safety information will be submitted to the IEC during the course of 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 conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki (3) and are consistent with ICH GCP (2) principles.

The Investigator or designee agrees to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IEC. The Investigator and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki 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, or for any other reason deemed necessary, an amendment to the ICF may be required. If a revision of the ICF is necessary, the Investigator or designee will, with the support of the Sponsor, ensure that the documents have been reviewed and approved by a relevant IEC before subjects are required to re-sign the ICF (including date and time). If new and important safety information is received, subjects who already completed or are discontinued from the study will be informed in writting.

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 (2). These guidelines apply specifically to pharmaceutical development, but nevertheless provide a robust and ethical framework for conducting a clinical study with products such as P3P. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki (3).

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 (4). 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 (5). Philip Morris International (PMI) 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), with the exception of nicotine, while providing an acceptable substitutes for cigarettes.

One of these products is P3P which is based on aerosolization of a nicotine containing powder that could satisfy smokers in terms of nicotine absorption similar to that of cigarettes. The aim of this study is to explore the nicotine absorption and subjective effects from four different variants of P3P and evaluate if these can provide an acceptable option to smokers as substitutes for cigarettes.

2.1.2 Description of the Product and Scientific Findings

P3P generates an inhalable aerosol from nicotine powder when air is drawn through it. P3P is a single use product that has a body in the form of a tube, similar to a cigarette, and contains a capsule. The capsule is pierced (activated) using a P3P piercing accessory before use. The P3P capsule contains nicotine powder composed of either solely nicotine salt or nicotine salt blended with mentholated flavor powder in a 4:1 ratio. The nicotine powder is generated by spray-drying nicotine, [redacted] and [redacted] The nicotine powder has a median particle size of 1.8 ± 0.2 µm or 2.25 ± 0.2 µm allowing deep lung deposition whereas the flavor particles have a particle size > 50 µm and deposit in the oropharyngeal cavity. A single P3P product contains 1 or 2 mg of nicotine, depending on the P3P variant. P3P is used in a similar way to cigarettes i.e. with a 2-step process with 1) puffing and 2) inhalation. The puffing step should be of sufficient intensity to trigger the spinning of the capsule.

An important factor to be optimized in order to achieve pulmonary delivery, while minimizing deposition of the aerosol in the oropharynx and upper airway, is the aerosol particle size. An aerosol comprising particles with diameters less than 5 µm is required for deep lung deposition and rapid absorption of nicotine. However, if the particles are very small (< 1 µm) they may be exhaled (6). Therefore, to achieve deep lung deposition while minimizing exhalation,

different variants of P3P with particle sizes in a respirable range (but higher than 1 μm) will be tested in this study.

In humans, there is no scientific data available to date on nicotine absorption following P3P use. However, nicotine absorption following the use of P3L has been studied in a clinical study in healthy adult cigarette smokers (7). P3L is another product developed by PMI that contains both nicotine and lactic acid like P3P, with the difference that these two components are in a liquid form. P3L generates inhalable nicotine-lactate aerosol formed by mixing and condensation of two gas streams resulting from the heating of nicotine and lactic acid present in a liquid, with the lactic acid acting as the carrier or aerosol forming vehicle. In the study, P3L PK parameters were compared to nicotine replacement therapy (Nicorette® inhalator). P3L provided peak plasma nicotine concentrations higher and faster compared to the Nicorette® inhalator with C_{max} of 9.7 ng/mL for P3L compared to 6.1 ng/mL for Nicorette® inhalator and T_{max} of 7 minutes for P3L versus 30 minutes for Nicorette® inhalator. The concentration-time profile supported a pulmonary route of nicotine absorption for P3L compared to the oromucosal absorption of Nicorette® inhalator (7). The PK profile of nicotine of P3L was comparable to the one for cigarettes (8).

Non-clinical information on P3P to support this clinical study is presented in the Investigator's brochure (IB) (9).

2.2 Purpose of the Study

The purpose of the study is to evaluate the PK profiles of four P3P variants (differing in nicotine powder particle size, nicotine concentration, and in the absence or presence of a flavoring system) following a fixed puffing regimen and an *ad libitum* use period. In addition, pharmacodynamic effects (subjective effects and related behavioral assessments) as well as human puffing topography will be evaluated, to provide further insights on product acceptance and product use. Safety will also be assessed throughout the study.

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 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 464 mL and does not exceed the levels for a standard blood donation. The risks related to blood sampling include for example: excessive bleeding, fainting, haematoma, 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

Although by product design, P3P does not generate toxins and carcinogens as observed with cigarette smoking (10), given the current state of knowledge of the product, it has not been demonstrated that P3P reduces the risk of developing smoking-related diseases compared to cigarettes.

Due to sensorial and technological differences between P3P 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. A confinement setting may also have an influence on puffing behavior and may lead to an increase of P3P use when *ad libitum* use is allowed.

An adult smoker using P3P 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 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 smoking abstinence 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 an AE(s)/SAE(s)

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained in detail to study subjects. Subjects will be informed that P3P has not currently been demonstrated to be less harmful than cigarettes. Unexpected malfunction of the P3P may lead to unforeseeable risk. Mitigation will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective and Endpoints

1. To evaluate the plasma concentration-time profile of nicotine and the derived PK parameters (with and without adjustment for baseline nicotine concentrations) of four P3P variants from the fixed puffing regimen.

   Endpoints:

   - Plasma nicotine concentration-time profile
   - Maximum plasma concentration [C_{max}]
   - Time to the maximum concentration [t_{max}]
   - Area under the concentration-time curve from start of product use ($T_{0\ fix}$) to 4 hours [$AUC_{fix\ (0\text{-}4h)}$]

3.2 Secondary Objectives and Endpoints

1. To evaluate the plasma concentration-time profile of nicotine and derived PK parameters (with and without adjustment for baseline nicotine concentrations) of the four P3P variants from the *ad libitum* use period.

   Endpoints:

   - Plasma nicotine concentration-time profile
   - Peak plasma nicotine concentration [C_{peak}]
   - Time to peak plasma nicotine concentration [t_{peak}]
   - Trough plasma nicotine concentration [C_{trough}]
   - Average of plasma nicotine concentration from $T_{0\ ad\ lib}$ to 1 hour [$C_{average}$]
   - Area under the concentration-time curve from start of product use ($T_{0\ ad\ lib}$) to 4 hours [$AUC_{ad\ lib\ (0\text{-}4h)}$]

2. To evaluate the pharmacodynamic effects (subjective effects and related behavioral assessments) of four P3P variants.

   Endpoints:

   - Visual Analogue Scale (VAS)-craving assessment from the fixed puffing regimen and *ad libitum* use period
   - Product evaluation by an adapted version of the modified Cigarette Evaluation Questionnaire (adapted mCEQ) following the *ad libitum* use period
   - Sensory Questionnaire (SQ) following the *ad libitum* use period

3. To evaluate human puffing topography of four P3P variants during the fixed puffing regimen and the *ad libitum* use period.

   Endpoints:

   - Per-puff parameters and per-product use experience parameters

4. To estimate the amount of powder aerosolized from P3P from the fixed puffing regimen and the *ad libitum* use periods.

   Endpoints:

   - Weight difference of P3P before and after use

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

   Endpoints:

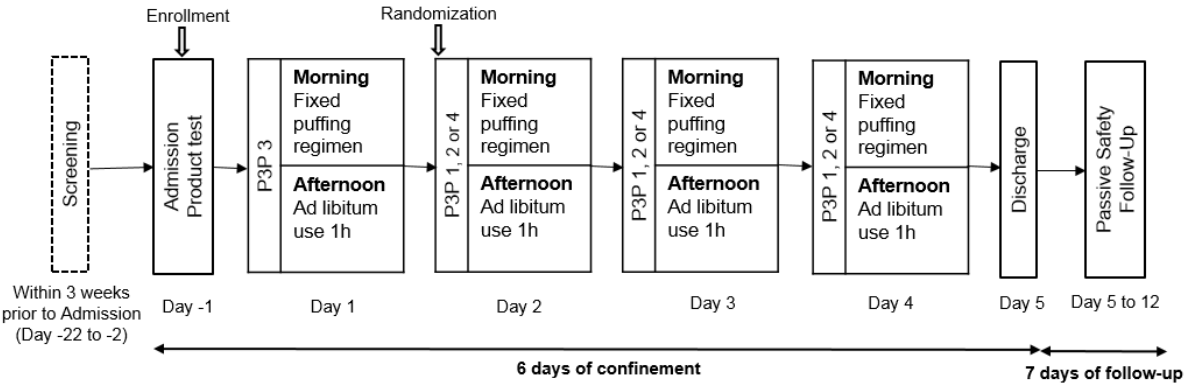
   - Incidence of adverse events (AEs), serious adverse events (SAEs)
   - Frequency of AEs, SAEs
   - Incidence of P3P product events including malfunction/misuse
   - Frequency of P3P product events including malfunction/misuse
   - Physical examination changes from baseline
   - Cough changes from baseline (VAS and three Likert scales)
   - Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, QTcB, QTcF intervals)
   - Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate)
   - Spirometry changes from baseline (FEV_1, FEV_1 % predicted, FVC, FVC % predicted FEV_1/FVC)
   - Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel
   - Concomitant medications

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a single-center, open-label, randomized, crossover study to evaluate the PK profiles of four P3P variants (differing in nicotine powder particle size, nicotine concentration and in the absence or presence of a flavoring system), (section 6.1), following a fixed puffing regimen and an *ad libitum* use period. In addition, PD effects (subjective effects and related behavioral assessments) as well as human puffing topography will be evaluated, to provide further insights on product acceptance and product use. Safety will also be assessed throughout the study.

Each subject will receive the four P3P variants starting with P3P 3, which has the lowest nicotine concentration, on Day 1 and continuing with P3P 1, P3P 2 and P3P 4 in a random order at the following assessment days (Figure 2). The subjects will be in confinement during the investigational period (Day -1 to Day 5).



P3P 1 characteristics: 2 mg nicotine; 2.25 µm nicotine powder particle size; unflavored
P3P 2 characteristics: 2 mg nicotine; 2.25 µm nicotine powder particle size; flavored
P3P 3 characteristics: 1 mg nicotine; 2.25 µm nicotine powder particle size; flavored
P3P 4 characteristics: 2 mg nicotine; 1.8 µm nicotine powder particle size; flavored

Figure 2 Study Flow Chart

The Screening Visit (Day -22 to Day -2)

A Screening Visit will be conducted within 3 weeks prior to Admission to the investigational site. Eligibility criteria will be verified at the Screening Visit (section 5.1). A demonstration of P3P (without product use) will be done by the investigational site staff.

The Admission Visit (Day -1)

Subjects will return to the investigational site for Admission (Day -1). Subjects should have been fasting for at least 6 hours prior to Admission. After confirmation of eligibility, subjects will be enrolled. All subjects that are not enrolled will be considered as screen failures. At

Admission, enrolled subjects will perform a product test using up to three P3P 3 products. After the product test, subjects not willing and/or unable to use P3P will be discontinued from the study. Subjects willing to continue their participation in the study after the product test will start their confinement phase.

The Confinement Period (Day -1 to Day 5)

On Day 1, after at least 10 hour abstinence from any tobacco/nicotine containing products, subjects will use P3P 3 during a fixed puffing regimen comprising of 12 puffs in total at a rate of one inhalation every 30 seconds (± 5 seconds) in the morning and during an *ad libitum* use period for 60 minutes (± 5 minutes) in the afternoon. The start of product use for fixed puffing and for the *ad libitum* use period will be defined as $T_{0\ fix}$ and $T_{0\ ad\ lib}$, respectively. There will be a washout period of at least 10 hours between $T_{0\ fix}$ and $T_{0\ ad\ lib}$.

A total of 10 blood samples will be taken for fixed puffing PK parameter estimation. One blood sample will be taken prior to the product use ($T_{0\ fix}$) 15 minutes ± 5 minutes (T-1). Thereafter in relation to $T_{0\ fix}$, blood will be drawn at the following time points: T1 after 2 minutes ± 1 minute, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, and T9 after 4 hours ± 5 minutes.

A total of 8 blood samples will be taken for the *ad libitum* PK parameter estimation. One blood sample will be taken prior to product use ($T_{0\ ad\ lib}$) at 15 minutes ± 5 minutes (T-1). In relation to $T_{0\ ad\ lib}$, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes and T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, and T7 after 4 hours ± 5 minutes.

PD effects related to craving will be assessed using a VAS scale at different timepoints. For the fixed puffing regimen the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ fix}$, all other assessments will be done after $T_{0\ fix}$, at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. For the *ad libitum* use period the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ ad\ lib}$, all other assessments will be done after $T_{0\ ad\ lib}$, at 10 minutes ± 2 minutes, at 20 minutes ± 2 minutes, 30 minutes ± 5 minutes, 40 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. VAS will be assessed immediately after the collection of the time-matching PK samples.

Product evaluation and sensory questionnaires will be assessed after the end of the *ad libitum* use period.

A puffing topography device will be attached to each P3P during both the fixed puffing regimen and the *ad libitum* use period. There will be one recording of HPT parameters per product use (section 7.9.1). Each P3P will be weighed before and after product use to estimate

the amount of nicotine delivered in the aerosol. The number of P3P used during the *ad libitum* use period will be recorded.

In the morning of Day 2, after confirmation that there are no safety concerns for each subject to continue in the study based on Investigator's judgement, 18 subjects will be randomized in order to cross-over the use of P3P 1, P3P 2 and P3P 4 (section 6.3).

Subjects discontinued before randomization will be replaced to reach 18 randomized subjects.

Subjects discontinued after randomization will not be replaced.

If a sufficient number of subjects are already randomized to the study sequences, any supernumerous subjects will be discontinued from the study prior to randomization only (section 5.2).

On Days 2, 3 and 4, subjects will be instructed to use the assigned P3P variant for the given study day for a fixed puffing regimen in the morning and an *ad libitum* use period in the afternoon as described for Day 1. On each study day including Day 1, start of product use should be at approximately the same time for fixed puffing in the morning and for *ad libitum* use in the afternoon with at least a 10 hour washout period between $T_{0\ fix}$ and $T_{0\ ad\ lib}$. There will be a washout of at least 10 hours following $T_{0\ ad\ lib}$ with respect to the $T_{0\ fix}$ of the morning of the following study day to allow adequate background correction of the nicotine plasma concentrations. The assessments performed on Days 2, 3 and 4 will be the same as those described for Day 1.

On Day 5, there will be no product use, but subjects will remain at the investigational site for additional PK blood sampling for the purposes of estimating the terminal elimination half-life. A total of 5 blood samples will be taken in relation to $T_{0\ ad\ lib}$ from the last product use at the following time points: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes, T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes and T5 after 24 hours ± 30 minutes.

Safety measurements including vital signs, ECG, safety laboratory parameters will be performed at several timepoints during the confinement period (Appendix A).

During confinement, the use of any tobacco and nicotine containing products, apart from product use assigned on the assessment days, will not be allowed. Use of tobacco and nicotine containing products will not be restricted once the subjects have left the investigational site.

The Safety Follow-Up Period (from Discharge or Early Termination plus 7 days)

After Discharge on Day 5 or early termination date, the subjects will enter a 7-day Safety Follow-Up Period during which AE/SAEs spontaneously reported by the subjects will be collected.

Any non-serious AE that is ongoing at the time of Discharge or early discontinuation will be followed-up by the Investigator or designee 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) or lost to follow up. At the end of the Safety Follow-Up Period, all ongoing non-serious AEs will be documented as "ongoing" and no further follow-up information will be sought for them by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly. All SAEs will be followed up by the Investigator or designee, despite their continuation, after the end of the 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).

SAEs reported after the end of the study and considered related to the investigational product by the Investigator must be captured and reported to UBC/PMI regardless of the time after end of the study.

All subjects discontinued from the study at any time after enrollment, will enter the 7 day Safety Follow-Up Period.

4.2 Rationale for Study Design

The minimum age of 21 years old in the inclusion criteria was selected based on the legal age of smoking in Switzerland (Canton of Ticino) of 18 years; and to account for the 3 years of smoking history.

Variants with two different nicotine contents (1 mg/product and 2 mg/product) will be tested. These two nicotine contents are evaluated in this study to identify which one would yield plasma nicotine concentrations as close as possible to those achieved after smoking a single cigarette. All of the subjects will initially use the lowest nicotine content product (P3P 3). The subject will be randomized to continue the study using the three remaining products (P3P 1, P3P 2 and P3P 4) containing 2 mg nicotine/product only on the Investigator's judgment who will be responsible to assess safety information following the use of P3P 3.

Two product use regimens: fixed puffing and *ad libitum* use will be applied to provide insight into nicotine absorption. The fixed puffing regimen with consistent use conditions across subjects will be applied in order to minimize variability and thereby provide a better understanding of the respective impact of nicotine content, particle size and presence or not of a flavoring system in the different P3P variants with regards to nicotine PK profile. The *ad libitum* use period will provide information on nicotine PK and product acceptance when subjects use the P3P according to their own puffing behavior which is closer to a real-world setting.

Sampling timepoints for determination of nicotine concentrations were selected to ensure reliable estimation of PK parameters. In particular, frequent sampling during the first 15 minutes from $T_{0\ fix}$ will be performed in order to reliably assess t_{max} which is expected to be around 7 minutes, similar to what was observed with P3L (7) and cigarettes (8), and compatible with absorption by the pulmonary route.

Plasma nicotine presents a biphasic profile, with a typical rapid initial disposition half-life ($t_{1/2\alpha}$) of 1.35 hours, followed by a slower terminal elimination half-life ($t_{1/2z}$) of 17 hours (11). To ensure a full nicotine washout between each product use, a separation of 3 days would have been required (~ 5 x elimination $t_{1/2z}$). Based on nicotine population PK modeling, it was estimated that subjects nicotine has entered in the terminal elimination phase with concentrations decreasing according to the terminal elimination rate constant (λ_z) after 8 to 10 hours post administration. As a consequence, a minimum of 10 hours have been established in this study design between the start of each use regimen to ensure appropriate washout of nicotine. Background-concentration correction will be applied to adjust for carry-over effects with adjustment of baseline values to the estimated $t_{1/2z}$ (or the terminal elimination rate constant λ_z) which will be derived from additional blood sampling on Day 5 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 oestrogen contraceptive (12). 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. CYP2A6 activity drives the metabolism of nicotine to 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 (8).

4.3 Appropriateness of Measurements

All laboratory measures utilized for this study are validated and are appropriate for the study assessments. Questionnaires used in this study, except craving VAS and cough questionnaires, are available as validated/previously published or adapted versions of validated questionnaires.

4.4 Study Duration

The entire study per subject will last 14 to 34 days. This will include a Screening period of up to 3 weeks prior to Admission (Day -22 to Day -2), 6 days of confinement (Day -1 to time of Discharge on Day 5), and a 7-days passive Safety Follow-Up (from time of Discharge at Day 5 until Day 12). The end of the study (EOS) for a subject is defined as either the Discharge at Day 5, or the date of early termination of the subject, plus the 7 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

5.1 Selection of Study Population

A sufficient number of eligible subjects will be enrolled and exposed to P3P 3 at Admission (Day -1) and Day 1 to ensure randomization of 18 subjects at Day 2. At least 8 subjects of each sex will be randomized to ensure each sex represents at least 40% of the randomized population.

5.1.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled into the study:

Inclusion Criteria	Rationale	Screening Visit	Admission Visit
1. Subject has signed the ICF and is able to understand the information provided in the ICF.	Administrative	X	
2. Smoking male or female aged between 21 and 65 years old.	Safety	X	
3. Subject is White.[a]	Effect	X	
4. Subject has been a smoker for at least the last 3 years prior to the Screening Visit.	Effect	X	
5. Has smoked ≥ 10 commercially available cigarettes per day for 4 weeks prior to Screening Visit. Smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).	Effect	X	
6. Subject does not plan to quit smoking within 2 months after Screening Visit.	Safety	X	X
7. 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).	Safety	X	
8. Availability for the entire study period and willingness to comply with study	Effect	X	X

Inclusion Criteria	Rationale	Screening Visit	Admission Visit
procedures, including smoking interruptions.			
9. Ready to accept using the P3P product.	Effect	X	

5.1.2 Exclusion Criteria

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

Exclusion Criteria	Rationale	Screening Visit	Admission Visit
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological and/or social reason).	Safety	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).	Administrative	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 clinically significant medical condition (including safety laboratory), which as per the judgment of the Investigator would jeopardize the safety of the subject.	Safety	X	

Exclusion Criteria	Rationale	Screening Visit	Admission Visit
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.	Effect	X	
5. Subject has donated or received whole blood or blood products within 3 months prior to Screening Visit.	Safety	X	
6. Subject has a BMI < 18.5 kg/m^2 or > 32.0 kg/m^2.	Safety	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.	Effect		X
8. Subject has a positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C.	Safety	X	
9. Subject has a positive alcohol breath test and/or a history of alcohol abuse that could interfere with the subject's participation in study.	Administrative	X	X
10. Subject has a positive urine drug test.	Administrative	X	X
11. Subject or one of their family members[b] is a current or former employee in the tobacco industry.	Administrative	X	
12. Subject or one of their family members[b] is an employee of the investigational site or of any other parties involved in the study.	Administrative	X	

Exclusion Criteria	Rationale	Screening Visit	Admission Visit
13. Subject has participated in another clinical study within 3 months prior to the Screening Visit. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study.	Safety	X	
14. Subject has been previously screened or enrolled in this study.	Administrative	X	
15. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission Visit) or is breastfeeding.	Safety	X	X
16. For women of childbearing potential only [c]: subject does not agree to use an acceptable method of effective contraception.[d]	Safety	X	X
17. Use of estrogen-containing hormonal contraception or hormone replacement therapy	Effect	X	X

[a] As defined by FDA guidance on Collection of Race and Ethnicity Data in Clinical Trials(1)

[b] 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"

[c] Women who are not of childbearing potential meet at least one of the following criteria:
Have undergone hysterectomy or bilateral tubal ligation,
Have medically confirmed ovarian failure, 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).

[d] Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception containing progesterone only, vasectomized partner(s) from Screening until the end of the Safety Follow-up Period. Hormonal contraception with estrogen containing products is NOT allowed in this study.

5.2 Discontinuation of Subjects from the Study

Discontinued subjects will include both subjects who withdraw from the study (subject's decision) or subjects who are discontinued from the study by the decision of the Investigator. 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 the 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 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 9.6) will be performed unless the subject refuses to perform the assessments. Early termination procedures are to be performed only for subjects who have been exposed to P3P. After the date of termination, the subject will enter into the 7-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 no longer justifies the subject's participation in this study.
- Positive pregnancy test (section 8.5).
- The Sponsor or Investigator terminates the study or the study terminates at a particular investigational site. If the Sponsor or the Investigator decides to prematurely terminate the study, the subject will be promptly informed. The head of the investigational site should report the fact and the reason in writing to the IEC.
- 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 to use P3P after the product test at Admission Visit. In such a situation, the subject will be discontinued immediately after the product test.
- Subject uses any tobacco or nicotine contaning product different from the assigned product during visits.

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

- Non-compliance to the study procedures based on the judgment of the Investigator.
- Sufficient number of subjects are already randomized to the study sequences. In this case, supernumerous subjects will be discontinued prior to randomization based on their screening number. Further details about the randomization process will be provided in a separate randomization plan.

Until randomization, subjects can be replaced, however subjects that discontinue the study after randomization will not be replaced.

5.3 Lost to Follow-Up

Reasonable number of attempts to contact the subject (including written correspondence and phone calls) should be done and documented in the source documents by the site. When the Investigator or designee(s) declare(s) a subject is 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 has lost track of 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 Selection Criteria

Any subjects who do not meet the entry criteria after signing the ICF and prior to Enrollment at Admission Visit will be considered as screen failures and will be replaced by other subjects. Re-screening of subjects will not be permitted.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

6.1.1 Investigational Products

P3P will be provided by the Sponsor and its distribution will be controlled by a qualified and appropriately trained designee.

P3P generates an inhalable aerosol from nicotine powder when air is drawn through it. P3P is a single use product that has a body in the form of a tube, similar to a cigarette, and contains a capsule. The capsule is pierced (activated) using a P3P piercing accessory before use. The P3P capsule contains nicotine powder composed of either solely nicotine salt or nicotine salt blended with mentholated flavor powder in a 4:1 ratio. The nicotine powder is generated by spray-drying nicotine, [redacted] and [redacted] The nicotine powder has a median particle size of 1.8 ± 0.2 µm or 2.25 ± 0.2 µm allowing deep lung deposition whereas the flavor particles have a particle size > 50 µm and deposit in the oropharyngeal cavity. A single P3P product contains 1 or 2 mg of nicotine, depending on the P3P variant.
The following P3P variants will be tested in this study and differ in nicotine powder particle size, nicotine concentration, and in the absence or presence of a flavoring system:

Table 1 P3P variants tested in this study

P3P variant	Nicotine content	Nicotine powder particle size	Total amount of nicotine/ product	Contains flavor particles
P3P 1	5%	2.25 ± 0.2 µm	2 mg	no
P3P 2	5%	2.25 ± 0.2 µm	2 mg	yes
P3P 3	2.5%	2.25 ± 0.2 µm	1 mg	yes
P3P 4	5%	1.8 ± 0.2 µm	2 mg	yes

6.1.2 Packaging and Labeling

The Sponsor will provide the P3P components separately. Assembly will be done at the investigational site (section 6.5.1). All parts will be packaged and labelled appropriately for on-site use. The capsules will be labelled with the necessary information for on-site use including, but not limited to, nicotine content, batch number, expiry date, indication that product is to be used for research purposes only, and storing conditions.

6.2 Use of Investigational Products

Subjects will never be forced to use P3P and will be free to stop using P3P at any time during the study.

6.2.1 Admission (Day -1)

After enrollment, subjects will be required to perform product test using up to three P3P 3 products. Subjects will be instructed to use P3P in a similar way to their own cigarette i.e. with a 2-step process with 1) puffing and 2) inhalation. They will be asked to puff with sufficient intensity to trigger the spinning of the capsule. The subject should hear the sound of the capsule spin and/or feel the vibration of the product induced by the spinning.

After the product test, subjects unable to use the product as specified (i.e. trigger the spinning of the capsule) as well as subjects not willing and/or unable to use P3P will be discontinued from the study and will enter a 7-day Safety Follow-Up Period.

6.2.2 Investigational Period (Day 1 to Day 5)

Each subject will use P3P 3 on Day 1. In the morning of Day 2, subjects will be randomized to one of six sequences in order to cross-over to the use of P3P 1, P3P 2 and P3P 4 on Days 2, 3 and 4 (section 6.3).

On each assessment day (Day 1 to Day 4), following at least 10 hours of abstinence from any tobacco and nicotine containing products, subjects will use the assigned product for the given visit with two product use regimen as described in Figure 2:

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

A puffing topography device will be attached to each P3P. There will be one recording of HPT parameters per product. Each P3P product will be weighed before and after product use to estimate the amount of nicotine delivered in the aerosol. During the *ad libitum* use period, the subjects can use the product according to their puffing behavior, without restrictions in the number of puffs, interpuff interval duration or number of products used. The number of P3P products used during the *ad libitum* use period will be recorded. The start and stop time of each product used during each puffing regimen will be recorded as well as the total number of puffs taken at the fixed puffing regimen.

The start of product use for fixed puffing and for the *ad libitum* use period will be defined as $T_{0\ fix}$ and $T_{0\ ad\ lib}$, respectively. There will be a washout period of 10 hours between $T_{0\ fix}$ and $T_{0\ ad\ lib}$.

There will be no product use on the Discharge day (Day 5).

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

Subjects will be continuously supervised by the investigational site staff during P3P use.

6.2.3 Safety Follow-Up Period

Use of the investigational product will not be permitted during the Safety Follow-Up Period. Subjects will be allowed to use their own cigarettes.

6.2.4 Stopping Rules for Investigational Product

For safety purposes, use of P3P should be temporarily reduced (decreasing number or/and intensity of puffs) or stopped in the event of any signs suggesting nicotine overexposure, e.g., gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach or abdominal pain), cold sweats, headache, dizziness and breathing problems, or any reasons at the discretion of the Investigator.

In the morning of Day 2 subjects will be randomized after confirmation that there are no safety concerns based on the Investigator's judgement.

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 9.6).

6.3 Method for Assigning Subjects to Sequence

On the morning of Day 2, after confirmation that there are no safety concerns for each subject to continue the study, 18 subjects will be randomized to one of the following six sequences of the remaining P3P variants in order to cross-over the use of P3P 1, P3P 2 and P3P 4 following a 2 Latin squares design balanced for first order carryover effects among the 3 variants.

Therefore, three subjects will be allocated to each sequence described in the table below:

Table 2 Description of sequences to allocate subjects to

Sequence	Day 2	Day 3	Day 4
1	P3P 2	P3P 4	P3P 1
2	P3P 4	P3P 1	P3P 2
3	P3P 1	P3P 2	P3P 4
4	P3P 1	P3P 4	P3P 2
5	P3P 2	P3P 1	P3P 4
6	P3P 4	P3P 2	P3P 1

Randomization to product exposure sequence will be done through sealed envelopes.

At least 8 subjects of each sex will be randomized to ensure each sex represents at least 40% of the randomized population.

If a sufficient number of subjects are already randomized to the study sequences, any supernumerous subjects will be discontinued from the study prior to randomization only (section 5.2).

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 prior to randomization.

6.4 Blinding

This study will be conducted as an open label study with no blinding. However, in order to prevent selection bias, Sponsor staff, Investigator, the subjects and the investigational site will be blinded to the randomization sequences until they are assigned. Subjects will not be informed of the complete sequence to which they have been assigned.

6.5 Investigational Product Accountability and Compliance

6.5.1 Assembly of Investigational Product

The Sponsor will provide the P3P piercing accessory, the P3P tube-shaped body and front plug and the P3P capsules according to local regulations.

The P3P capsule should be inserted in the P3P body no earlier than 2 hours prior to product use and the assembled product should be activated by piercing the capsule immediately before product use.

Responsibility for assembly and activation of the investigational product will be held by the investigational site pharmacist or other adequately trained investigational site collaborator.

6.5.2 Dispensing Investigational Products

From Day -1 until Day 4, the assembled and activated P3P products will be dispensed by the investigational site collaborator, as per the study design. Each dispensing of the investigational product to the subject will be recorded in a log.

6.5.3 Storage and Accountability

The P3P components will be stored in a secured storage place at the investigational site with access limited to the authorized personnel only. Full accountability of the distributed products will be ensured by designated site staff. Subjects will return each P3P product immediately after use to the investigational site personnel for accountability and product weighing (section 7.9.2).

6.5.4 Investigational Products Retention

Used and unused P3P products will be destroyed or returned to the Sponsor upon study completion.

6.5.5 Compliance to Investigational Products

Compliance will be ensured by strict distribution of the products (product by product) and collection of any used and unused investigational product by the designated site staff.

6.6 Restrictions

6.6.1 Smoking Restrictions

During the Screening period, subjects will be allowed to smoke according to their smoking habits except during the procedures of the Screening Visit (section 9.1). During confinement (from Admission to Discharge or early termination), smoking or use of any tobacco or nicotine-containing products, except the allocated P3P on the assessment days, will not be permitted. A washout period of at least 10 hours should be respected before product use at Day 1 and before the start of each product use regimen (ie. at least 10 hours washout between $T_{0\ fix}$ and $T_{0\ ad\ lib}$ and vice versa).

6.6.2 Dietary and Activity Restrictions

A standard diet will be designed for the whole confinement period. For each meal, the caloric and fat content should be controlled in order to avoid a "high-fat" diet. The FDA guidance on food-effect studies for bioequivalency 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) (13)."

Subjects are not allowed to bring their own food or beverages to the investigational site. Meals will be served according to the schedules provided 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 the product use periods) as long as 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. Fasting state has to be observed for at least 6 hours prior to blood drawings for the safety laboratory at Admission, and on Days 2, 3, 4 and 5.

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

6.6.3 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.

Use of hormonal contraception containing estrogens and hormone replacement therapy are prohibited and are considered an exclusion criterion. Only hormonal contraception with products containing progesterone is allowed during this study.

Any medication with an impact on the CYP2A6 metabolism (as prescription and over-the-counter products), including, but not limited to medication listed in Table 3, 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 Admission 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 must not be used during the entire study until the time of Discharge or early termination. Prior to database lock, concomitant medication will be reviewed according to their potential impact on CYP2A6 activity and assessed for their potential impact on the study results.

Table 3 CYP2A6: Substrates, Inhibitors, and Inducers (14)

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

Use of over the counter medication will be restricted during confinement, 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 medications used will be fully documented (for details see section 7.4.4).

7 STUDY PROCEDURES

Site personnel performing or recording study assessments must have the appropriate and fully documented training. An overview of all study assessments 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

Prior to any study assessment being performed, 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, Smoking Cessation Advice and Product Debriefing

At Screening, Admission and Discharge all subjects will receive 1) information on the risks of smoking, 2) smoking cessation advice, and 3) debriefing on P3P.

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 (15). The debriefing of subjects on P3P will address any intended or unintended beliefs that participants may have about P3P. The goal of the debriefing is to help ensure that subjects enter and exit the study with an accurate understanding of the product risks, including an understanding that P3P has not currently been demonstrated to be less harmful than cigarettes.

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 Smoking Abstinence/Periods of Reduced Smoking

Subjects will be offered support during periods of smoking abstinence while confined to the investigational site. Support will be given by the Investigator and investigational site staff. Support resources will include counselling and assistance, distraction, 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 and race will be recorded for each subject at Screening Visit.

7.4.2 Smoking History

At Screening Visit, subjects will be asked the following questions about their smoking history and habits:

1. Have you smoked for at least the past 3 years?
2. How many years have you smoked?
3. On average, how many cigarettes per day have you smoked since you started smoking?
4. A. On average, how many cigarettes per day have you smoked over the last 4 weeks?
   B. Of these, on average per day, how many were menthol cigarettes?
5. What brand of cigarettes do you smoke?

This self-reported daily consumption of cigarettes at the Screening Visit will be used to assess eligibility for the study.

At the Screening Visit the subject will also be asked if he/she is planning to quit smoking in the next 2 months i.e. before completion of the study.

Furthermore, subjects will be asked if they are ready for 6 days of smoking interruption. Only subjects prepared and able to comply with this requirement will be considered for participation in the study.

7.4.3 Demonstration and P3P Test

All subjects will have a demonstration of P3P (without product use) at the Screening Visit.

At Admission, after enrollment, subjects will be required to perform a product test using up to three P3P 3 products. Subjects will be instructed to use P3P in a similar way to their own cigarette i.e. with a 2-step process with 1) puffing and 2) inhalation. They will be asked to puff with sufficient intensity to trigger the spinning of the capsule. The subject should hear the sound of the capsule spin and/or feel the vibration of the product induced by the spinning.

After the product test, subjects unable to use the product as specified (i.e. trigger the spinning of the capsule) as well as subjects not willing and/or unable to use P3P will be discontinued from the study and will enter a 7-day Safety Follow-Up Period.

7.4.4 Medical History, Concomitant Disease, Previous and Concomitant Medications

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

Medication taken within 4 weeks prior to 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 prescription 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.

7.4.5 Physical Examination

Physical examination will be conducted at Screening, Admission and at the day of Discharge or at early termination.

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

7.4.6 Body Height and Weight

Body height and weight will be recorded at the Screening Visit and 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.

7.4.7 Vital Signs

Vital signs (systolic and diastolic blood pressure, respiratory rate and pulse rate) will be measured at Screening Visit, Admission and on every day of confinement (Day 1 to Day 5). On Day 1 to Day 4, vital signs will be assessed within 60 minutes prior to product use and 60 minutes ± 10 minutes after each product use period (fixed puffing regimen and *ad libitum* use).

All parameters will be recorded in supine position after the subject has rested for at least 5 minutes. At Screening and Admission, the subject should have abstained from smoking for at least 15 minutes prior to measurement.

7.4.8 Other Clinical Assessments

7.4.8.1 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position at Screening, Admission and on every day of confinement (Day 1 to Day 5). During the investigational product-use days (Day 1 to Day 4) ECG will be recorded after the fixed puffing regimen and after the *ad libitum* use. 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 Bazett's formula and Fridericia's formula. Every ECG has to be assessed as normal, abnormal – clinically not significant, or abnormal – clinically significant. A diagnosis has to be provided in the CRF for all ECGs assessed as abnormal – clinically significant. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents.

7.4.8.2 Spirometry

Spirometry without bronchodilator will be performed at Screening Visit and Discharge in accordance with the 2005 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry (16). Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set (17).

Assessed parameters will include: FEV_1, FEV_1 % predicted, FVC, FVC % predicted, 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 having stopped using cigarettes (Screening Visit).

7.5 Biomarker Assessment

7.5.1 Biomarkers of Exposure to Nicotine

For PK analysis of plasma nicotine levels, venous blood samples will be obtained according to the investigational site standard operating procedures (SOPs) at the following timepoints:

a) Fixed puffing (Morning: Days 1 through 4):

A total of 10 blood samples will be taken for fixed puffing PK parameter estimation. One blood sample will be taken prior to the product use ($T_{0\ fix}$) 15 minutes ± 5 minutes (T-1). Thereafter in relation to $T_{0\ fix}$, blood will be drawn at the following time points: T1 after 2 minutes ± 1 minute, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1

minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, and T9 after 4 hours ± 5 minutes.

b) *Ad libitum* use (Afternoon: Days 1 through 4):

A total of 8 blood samples will be taken for the *ad libitum* PK parameter estimation. One blood sample will be taken prior to product use ($T_{0\ ad\ lib}$) at 15 minutes ± 5 minutes (T-1). In relation to $T_{0\ ad\ lib}$, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes and T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, and T7 after 4 hours ± 5 minutes.

c) Day of Discharge (Day 5)

A total of 5 blood samples will be taken on Day 5. Blood samples will be taken in relation to $T_{0\ ad\ lib}$ from Day 4 at the following time points: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes, T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes and T5 after 24 hours ± 30 minutes.

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

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.

7.5.2 CYP2A6 Activity

CYP2A6 activity will be assessed on Day 1 prior to P3P use. CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites. In this study the CYP2A6 activity will be measured in plasma using the metabolic molar ratio of *trans*-3'-hydroxycotinine/cotinine.

7.6 Laboratory Assessments

7.6.1 Clinical Chemistry, Hematology, and Urine Analysis Safety Panel

A blood sample for hematology and clinical chemistry analysis will be taken from each subject at Screening, Admission and Day 2 to Day 5. Subjects should be fasting for at least 6 hours prior to sampling, except at Screening where non-fasting samples can be used. Tests will be conducted at a local laboratory (Appendix B). A urine sample will also be collected from each subject for urine analysis. Parameters to be tested are listed in Table 4.

Table 4 Clinical Laboratory Parameters for Safety Panel

Hematology	Clinical Chemistry	Urine Analysis

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

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

7.6.2 Serology

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

7.6.3 Urine Drug Screen

A urine drug screen will be performed at the site at Screening and Admission. The urine will be screened for amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates.

7.6.4 Urine Cotinine Screening

A urine dip-stick cotinine test will be performed at Screening in order to confirm the subject's smoking status. The test must detect cotinine with a threshold of ≥ 200 ng/mL, (e.g., One-Step Cotinine Test 008A086, Ultimed, Belgium).

7.6.5 Alcohol Breath Test

An alcohol breath test will be conducted using an alcometer device at Screening and Admission.

7.6.6 Urine Pregnancy Test

A urine pregnancy test will be performed for all female subjects at Screening, Admission and at Discharge. Subjects with a positive urine pregnancy test at the Screening or Admission Visits will not be enrolled and 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.

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

7.7 Sample Handling, Storage, and Shipment

Participating laboratories for blood samples testing and safety laboratory samples testing are listed in Appendix B. Urine drug screen, breath alcohol screen, urine pregnancy tests and urine cotinine tests will be done by the site personnel at the site.

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. 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. Subjects should be in a seated position during blood collection.

In total, around 464 mL will be drawn for this study including samples for determination of nicotine concentrations, CYP2A6 activity and safety. This calculation is based on an individual volume of each sample of 5 mL for nicotine PK (of which 4 mL is needed for nicotine dosing and 1 mL for cannula rincing of saline solution as per site's SOPs), 4 mL for CYP2A6 analysis and 12.5 mL for safety laboratory assessments. The total volume of blood drawn will not exceed the levels for a standard blood donation.

More details on the procedures for collection, labeling, handling and shipment of samples are described in a separate SHM.

7.8 Questionnaires

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

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

7.8.1 Fagerström Test for Nicotine Dependence

Potential nicotine dependence will be assessed via a subject self-reported questionnaire at Screening using the Fagerström test for nicotine dependence (FTND) in its revised version (18).

The questionnaire consists of six questions that will be answered by the subject. The scores obtained allow the classification of nicotine dependence in three different levels: mild (0-3 points), moderate (4-6 points), and severe (7-10 points).

7.8.2 Visual Analogue Scale for Craving

A VAS-craving assessment will be used to assess the level of craving of the subject based on their response to the question, "How strong is your craving for cigarettes?" on a scale of 0 (no craving) to 10 (strong craving) (19).

The VAS craving will be completed by the subject at Days 1 to 4. For the fixed puffing regimen the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ fix}$, all other assessments will be done after $T_{0\ fix}$, at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each.

For the *ad libitum* use period the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ ad\ lib}$, all other assessments will be done after $T_{0\ ad\ lib}$, at 10 minutes ± 2 minutes, at 20 minutes ± 2 minutes, 30 minutes ± 5 minutes, 40 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each.

Questionnaires are to be completed after blood samples have been taken.

7.8.3 Adapted Version of the Modified Cigarette Evaluation Questionnaire

An adapted mCEQ will be completed by each subject within 60 minutes after the *ad libitum* use session on Days 1 through 4.

The questionnaire to be used adapts the wording of mCEQ items (20) to RRPs, following a similar approach with the Product Evaluation Scale (21) which is an adaptation of the mCEQ for oral tobacco products.

The questionnaire assesses the degree to which subjects experience the reinforcing effects of P3P 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)

7.8.4 Sensory Questionnaire

A sensory questionnaire (SQ) will be completed by each subject within 60 minutes after the *ad libitum* use session on Days 1 through 4 (adapted from (22)). The SQ assesses the subject's opinion on the following sensory parameters:

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

7.8.5 Cough Assessment

Subjects will be asked if they have experienced a regular need to cough, e.g., whether they have coughed several times in the previous 24 hours prior to assessment. If the answer is 'yes', they will be asked to complete a cough assessment questionnaire (which includes a VAS, three Likert scales, and an open question).

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

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

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

  1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe.
- The frequency of cough will be assessed on a 5-point Likert scale ranging from 1 to 5:

  1 = rarely; 2 = sometimes; 3 = fairly often; 4 = often; 5 = almost always.
- The amount of sputum production will be assessed on a 4-point Likert scale ranging from 0 to 3:

  0 = no sputum; 1 = a moderate amount of sputum; 2 = a larger amount of sputum; 3 = a very large amount of sputum.

Cough assessment will be conducted at Admission prior to product test and 24 hours (±1 hour) after product use ($T_{0\ fix}$) for each variant (Day 2 through Day 5). Cough assessment should be done in the morning prior to any product use.

7.9 Other Study Procedures

7.9.1 Human Puffing Topography

Human puffing topography involves the measurement of each subject's unique way of using P3P using the HPT SODIM® device. The HPT SODIM® device, model SPA/M (SODIM® Instrumentation, Fleury les Aubrais, France) is a device which is used to measure puffing topography. It consists of a special sample holder with mechanical adapter and a data logger. Both the sample holder and the mechanical adapter are associated prior the activation of the P3P, and its insertion into the mechanical adapter using a depth adjustment tool. The sample holder is connected by 2 narrow tubes to the portable data logger/recording system. Any malfunction of the HPT SODIM® portable device will be documented in the appropriate log.

The HPT SODIM® device has to be used for every P3P used for all subjects from Day 1 to Day 4, both during the fixed puffing and the *ad libitum* use period. For each subject, one HPT Device will be assigned at Day 1 which will be used by that subject for all 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 HPT SODIM® device to the site collaborators which will be responsible for the HPT assessment. All HPT SODIM® devices will be returned to the Sponsor after completion of the study.

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

Prior to calculation of the per-product use 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.

7.9.2 Weighing of P3P Products

From Day 1 to Day 4, each P3P used should be weighed before product use (after assembly) and as early as possible (but within maximum 75 minutes) after the end of product use. The pre- and post- product use weight and time of weighing will be recorded in the CRF.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) is defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product or a study procedure, whether or not related to the product or the study procedure. Careful Investigator's 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.

8.1.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate 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 (concomitant disease), and whose severity or frequency 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 whose severity or frequency increased after that point is to be captured as an AE or SAE, depending on the seriousness criteria met.

8.2 Collection and Reporting of Adverse Events

8.2.1 Collection of Information

Any non-serious AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's 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.

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

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

During a 7-day Safety Follow-Up Period there will be recording of spontaneously reported new AEs/SAEs and follow-up of ongoing AEs/SAEs 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.

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.

SAEs spontaneously reported to the Investigator after the end of the Safety Follow-Up Period and considered related to the investigational product must also be reported to the sponsor.

8.2.3 Intensity of Adverse Event

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

Table 5 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 requires medical intervention

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

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

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

Related: The temporal relationship of the adverse event to IP 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 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 about the IP P3P in section 6.5 of the current Investigator's Brochure (9).

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).

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

All SAE will be followed up by the Investigator or designee, despite their continuation 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).

8.3 Reporting of Serious Adverse Events

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

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

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

UBC Pharmacovigilance:	Fax number:	[redacted]
	E-mail:	[redacted]
	Address:	United BioSource Corporation [redacted]

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 UBC Pharmacovigilance according to the same timelines 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 local IEC, 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 CTCAE version 4.03 grading scales (Appendix C). 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. 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.

Subjects with clinically significant abnormal laboratory values at Screening will not be enrolled. Abnormal laboratory test results detected at the Screening Visit whose CTCAE grades are 2 or higher or still are CTCAE grade 1 and deemed clinically significant are usually concomitant disease or a manifestation of one and must be recorded accordingly. However, in some instances, they may be assessed as AEs (and therefore must be handled according to the directions 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 be either recorded as AEs (and handled according to the directions in section 8.2) or linked to a concomitant disease or still to an already reported AE.

The principles for assessing and reporting abnormal laboratory test results, emerging after the Screening Visit, using CTCAE 4.03 grading scales are set up in Table 6:

Table 6 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.

§ grade increase in this context means the value is higher than the one from the Screening Visit.

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 the clinical significance by the Investigator/designee based on his/her medical judgement. All abnormal clinical significant test results or clinical examination findings can, at the discretion of the Investigator, be reported as AEs and handled according to the directions from section 8.2.

8.5 Reporting and Follow–Up of Pregnancies

8.5.1 Period of Collection and Follow-up

Pregnancies detected between the time of signature of the ICF and 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.

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

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

8.5.2 Reporting of Pregnancies

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

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

The Investigator is responsible for informing the corresponding IEC of the 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 9.6), as soon as practical after discontinuation and will enter the 7-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 P3P malfunction or misuse (use not in accordance with its instruction) by a subject will be documented by the Investigator using a Product Issue Log. Information regarding product malfunction or misuse should be actively collected during the study visits.

Furthermore, any malfunction or misuse of P3P that leads to an AE/SAE will follow the same processes as described above.

9 STUDY ACTIVITIES

A detailed schedule of all study activities and assessments is provided in Appendix A. Measurements not conducted at the exact time point indicated, 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 procedure is provided, then the procedure can be performed at any time during the day.

9.1 Screening Visit

The Screening Visit will be performed within 3 weeks prior to Admission. 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 7.

Table 7 Time Schedule – Screening Visit

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Prior to any other procedure		Collection of informed consent	
		Information on risks of smoking, smoking cessation advice and product debrief	
		Smoking history/habits questionnaire	
		FTND questionnaire	
		Demographic data	
		Medical history/ concomitant disease	
		Prior (within 4 weeks prior to Screening) and concomitant medication	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		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 smoking abstinence 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 smoking. After resting in sitting position for at least 15 minutes prior to testing.
	✓	Clinical laboratory parameters (hematology, clinical chemistry)	
		Collection of spot urine for: - Urine analysis safety panel - Urine drug screen - Urine cotinine screen - Urine pregnancy test (all female subjects)	
	✓	Serology	HIV 1/2, Hepatitis B and C
		Alcohol breath test	
During the visit		Review of inclusion/exclusion criteria based on all relevant assessments	Includes readiness to comply to study procedures, including smoking interruptions; intention to quit smoking in the next 2 months
		P3P 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; FTND = Fagerström Test for Nicotine Dependence; HIV = Human immunodeficiency virus; SAE = Serious adverse event.

9.2 Admission Visit

The assessments performed at Admission are listed in Table 8.

Table 8 Time Schedule – Admission Visit

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Before enrollment		Information on risks of smoking, smoking cessation advice and product debrief	
		Concomitant medication	
		Physical examination	
		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement. At least 15 minutes smoking abstinence prior to measurement.
		ECG	After resting for at least 10 min in supine position prior to recording.
		Urine drug screen	
		Urine pregnancy test (all female subjects)	
		Alcohol breath test	
		Review of Inclusion criteria 6 and 8 and exclusion criteria 7, 9, 10, 15, 16 and 17	
		Enrollment	
	✓	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 6 hours of fasting.
		Urine analysis safety panel	
		Cough assessment	VAS, Likert and open question
After enrollment		P3P product test by subject	Using up to three P3P 3 products
After product test		Collection of used products	
During the visit		AE/SAE recording	
During the visit		Product events malfunctions/misuse	

Abbreviations: AE = Adverse event; ECG = Electrocardiogram; SAE = Serious adverse event; VAS = Visual analogue scale

9.3 Investigational Period (Day 1 to Day 4)

At each assessment day subjects will use the assigned product for the given visit with two product use regimen:

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

The study activities performed in the morning (prior to and related to fixed puffing) for Days 1, 2, 3 and 4 are listed in Table 9. The study activities performed in the afternoon (related to *ad libitum* product use and post product use activities) are listed in Table 10. The start of each product use regimen will be separated by at least 10 hours.

Table 9 Time Schedule – Fixed puffing period (Day 1, 2, 3, 4 - Morning)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Prior to product use	✓	Blood sampling for CYP2A6 assessment	Day 1 only
Prior to product use	✓	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 6 hours of fasting. Day 2, 3 and 4
Prior to product use		Urine analysis safety panel	Day 2, 3 and 4
Prior to product use		Cough assessment	Day 2, 3 and 4. 24 ± 1 hour after $T_{0\ fix}$ for the product used on the previous day
Prior to product use at Day 2		Randomization	Day 2 only. Discontinuation of supernumerous subjects, if applicable, should occur prior to randomization
Prior to product use (within 2 hours)		Assembly and weighing of product	
Prior to product use (within 1 hour)		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.
15 ± 5 minutes prior to $T_{0\ fix}$	✓	Blood sampling for baseline nicotine level for fixed puffing	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
15 ± 5 minutes prior to $T_{0\ fix}$		VAS-craving: baseline for fixed puffing	
Just before product use		Piercing of P3P capsule	
Start of product use: $T_{0\ fix}$		Product use (fixed puffing) with HPT recording	After at least 10 hours of nicotine washout. Day 1: P3P 3 Day 2, 3 and 4: P3P 1, 2 and 4. One product variant used at a given visit. The order depends on the sequence a subject was randomized to. 1 puff every 30 seconds, 12 puffs in total
During/after fixed puffing product use	✓	Blood sampling for fixed puffing nicotine PK assessment	Post $T_{0\ fix}$, blood will be drawn at the following time points: T1 after 2 minutes ± 1 minute, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, T9 after 4 hours ± 5 minutes.
During/after fixed puffing product use		VAS-craving	Post $T_{0\ fix}$, craving will be assessed at the following time points 4 minutes (± 2 minutes) 10 minutes (± 2 minutes) 15 minutes (± 2 minutes) 30 minutes (± 5 minutes) 1 hour (± 10 minutes) 2 hours (± 10 minutes) 4 hours (± 10 minutes)
Between 30 minutes and 2 hours after $T_{0\ fix}$		Breakfast	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
60 ± 10 minutes post fixed puffing		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.
Within 75 min after product use		Collection and weighing of used product	
After fixed puffing product use		ECG	After resting for at least 10 min in supine position prior to recording.
After the end of blood sampling for fixed puffing PK		Lunch	
		Nicotine washout	At least 10h between $T_{0\ fix}$ and $T_{0\ ad\ lib}$
During washout		Optional: snacks	
Ongoing		Support during period of smoking abstinence	
Ongoing		AE/SAE, concomitant medication recording	
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

Table 10 Time Schedule – *Ad libitum* use period (Day 1, 2, 3, 4 - Afternoon)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Prior to product use (within 2 hours)		Assembly and weighing of products for *ad libitum* use	
15 ± 5 minutes prior to $T_{0\ ad\ lib}$	✓	Blood sampling for baseline nicotine level for *ad libitum* use	
15 ± 5 minutes prior to $T_{0\ ad\ lib}$		VAS-craving: baseline for *ad libitum* use	
Just before each product use		Piercing of P3P capsule	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Start of product use: $T_{0\ ad\ lib}$		Product use (*ad libitum* for 1 hour) with HPT recording	After at least 10 hours of nicotine washout. At each day the same product which is used for fixed puffing in the morning will be used for the 1 hour *ad libitum* session in the afternoon.
During/after *ad libitum* product use	✓	Blood sampling for nicotine PK assessment from the *ad libitum* use	Post $T_{0\ ad\ lib}$, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes, T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, T7 after 4 hours ± 5 minutes.
During/after *ad libitum* product use		VAS-craving	Post $T_{0\ ad\ lib}$, craving will be assessed at the following time points 10 minutes (± 2 minutes) 20 minutes (± 2 minutes) 30 minutes (± 5 minutes) 40 minutes (± 5 minutes) 1 hour (± 10 minutes) 2 hours (± 10 minutes) 4 hours (± 10 minutes)
Within 75 min after start of product use ($T_{0\ ad\ lib}$)		Collection and weighing of used products	
Within 60 minutes after the end of *ad libitum* product use		Adapted mCEQ	
Within 60 minutes after the end of *ad libitum* product use		Sensory Questionnaire	
60 ± 10 minutes after the end of *ad libitum* product use		Vital signs (blood pressure, pulse rate, respiratory rate)	At least 5 min in supine position prior to measurement.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
		ECG	After resting for at least 10 min in supine position prior to recording.
Between 30 minutes and 2 hours after $T_{0\ ad\ lib}$		Evening meal	
Ongoing		Support during period of smoking abstinence	
Ongoing		AE/SAE, concomitant medication recording	
Ongoing		Product events malfunctions/misuse	

Abbreviations: Adapted mCEQ; Adapted version of the modified Cigarette Evaluation Questionnaire; AE = Adverse event; ECG = Electrocardiogram; HPT = Human puffing topography; PK = Pharmacokinetic; SAE = Serious adverse event; VAS = Visual analogue scale

9.4 Day of Discharge

The assessments in Table 11 will be conducted prior to the time of Discharge on Day 5:

Table 11 Time Schedule – Day of Discharge (Day 5)

Blood Sample	Procedures	Additional Information
	Support during periods of smoking abstinence	Ongoing
✓	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 6 hours of fasting.
	Urine analysis safety panel	
	Cough assessment	24 ± 1 hours after $T_{0\ fix}$ for the product used on the previous day
	Breakfast	
✓	Blood sampling for determination of subject's nicotine $t_{1/2z}$	Blood will be drawn at the following time points post $T_{0\ ad\ lib}$ for the product used on Day 4: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes,

Blood Sample	Procedures	Additional Information
		T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes, T5 after 24 hours ± 30 minutes.
	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.
	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 risks of smoking, smoking cessation advice and product debrief	
	AE/SAE, concomitant medication recording	
	Discharge	

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

9.5 Safety Follow-Up Period

After Discharge on Day 5 or at the time of early discontinuation all enrolled subject will enter a 7-day Safety Follow-Up Period during which new AE/SAEs spontaneously reported by the subject will be collected. The follow-up of ongoing AEs/SAEs will be conducted by the study investigational site as described in section 8.2.6.

9.6 Early Termination Procedures

When a subject is discontinued from the study, all early termination procedures listed below are performed unless the subject refuses to perform the assessments.

Table 12 Time Schedule – 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 risks of smoking, smoking cessation advice and product debrief	
	AE/SAE, concomitant medication recording	
	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 IEC may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data 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 referenced documents.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

With the exception of the subject-reported outcome data, all results from the clinical assessments will be recorded in the source documents by the Investigator or their authorized designee(s) and then transcribed into the CRFs at the investigational site. The subject questionnaires and the VAS will be entered by the subject directly in a paper copy. Trained study personnel will be responsible for capturing the data from the observations, tests and assessments specified in the protocol in the source documents and then transferring the data into the CRF, in accordance with the 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 corrections made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change and identification of the person making the change. The CRF for each subject will be checked against the source documents at the 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 deviations from the procedures defined in this document, including but not limited to, any violation of inclusion/exclusion criteria, mis-randomizations, 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 drugs 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 will be used to assess protocol deviations from the data programmatically. Protocol deviations will be reconciled prior to closing the study and locking the clinical database.

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 CRF database. The overall procedure for managing protocol deviations are defined in the SOPs and study specific procedures of the CRO data management team. All deviations will be reviewed, as determined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

11.2 Data Handling

All study data will be managed by the data management CRO (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. This document will describe, in detail, the procedures and processes related to data management.

All data of all subjects that sign the ICF will be captured and stored in the study database. For Screen Failuers 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). Discrepancy will be identified manually as well as systematically, and data clarification forms (DCFs) will be issued to the investigational site, as necessary.

Data queries will be raised for discrepant or missing data. All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

Adverse events, 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 medications:	WHO Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical classification system

11.2.3 Database Lock

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

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

Any changes to the database after that time can only be made by written agreement between the Sponsor and the data management and statistical team at the CRO. Any of those changes must be documented in the database log file.

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 Data Structure Specifications.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Full details of the statistical analysis will be given in a detailed 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 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 detailed in the SAP.

12.1.2 Definitions for Statistical Data Analysis

For PK/PD analysis, baseline will be defined as the last assessment prior to $T_{0\ fix}$ (15 minutes prior to $T_{0\ fix}$) during fixed puffing regimen, and as the last assessment prior to $T_{0\ ad\ lib}$ (15 minutes prior to $T_{0\ ad\ lib}$) during *ad libitum* use, for each study day of exposure.

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by product variant, 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 will be presented instead of arithmetic mean and SD.

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 and overall, and separately for fixed and *ad libitum* use regimen when applicable.

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, 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), i.e.,

preceded by a ">", for example ">xx," the numerical xx will be used for calculation and reporting in summary tables.

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

The sample size is empirically based, as there is no prior information on which to base it, and as there are no considerations for statistical hypothesis.

As per study design P3P 3 is the first product variant used by all subjects at Day 1 for safety reasons (i.e P3P 3 has the lowest nicotine concentration of all P3P variants). As a result, only the 3 remaining product variants will be randomized over Day 2-4, which leads to 6 possible sequences. Considering that this study is a pilot investigation, and that we are expecting a low drop-out rate, 3 subjects will be allocated to each sequence. Therefore, 18 subjects will be randomized.

A sufficient number of eligible subjects will be enrolled and exposed to P3P 3 at Admission (Day -1) and Day 1 to ensure randomization of 18 subjects to one of six possible sequences at Day 2.

12.3 Analysis Populations

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

12.3.1 Pharmacokinetic Population

The nicotine exposure analysis sets consist of all the enrolled subjects who gave informed consent, completed at least one of the single use of P3P, and for whom at least one primary nicotine PK parameter can be derived. Only subjects without major protocol deviations will be included in the nicotine exposure analysis sets.

12.3.2 Safety Population

The safety set population, consists of all the subjects who give informed consent, have at least one exposure to P3P (including the product test at Admission [Day -1]) and have at least one safety assessment.

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 safety populations, if there is at least a difference of 3 subjects between the populations.

Summaries will include sex, age, height, weight and BMI, smoking 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 Primary Objectives and Endpoints

12.5.1 Primary Endpoint Analysis Variables

PK endpoints are listed in section 3.1.

Nicotine PK parameters for fixed puffing regimen will be derived from plasma nicotine concentration versus time data using a non-compartmental analysis (NCA) technique using Phoenix WinNonlin, Version 7.0 or higher.

To minimize the carry-over effect in the nicotine plasma PK parameters due to limited washout periods (see Section 4.2), background-concentration correction will be applied to the concentration data for the fixed puffing regimen and *ad libitum* use. The baseline correction will be implemented by calculating the nicotine exposure parameters using adjusted concentration values as described below.

The nicotine terminal elimination rate constant λ_z (and $t_{1/2z}$) will be estimated from the Day 5 PK samples 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 excluding the concentration at t_{max}), consistent with the assessment of a straight line on the log- transformed scale. The nicotine plasma background-corrected PK parameters will be derived by performing the NCA on the corrected concentrations.

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

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:

cC_{max}	Background-corrected maximum observed plasma concentration. cC_{max} will be reported as long as there is at least one quantifiable concentration post-exposure
t_{max}	Time to maximum concentration C_{max} during fixed puffing regimen
$cAUC_{fix(0-4h)}$	Background-corrected area under the plasma concentration-time curve from start of product use ($T_{0\ fix}$) to 4 hours [$cAUC_{fix\ (0-4h)}$]

Unadjusted PK parameters will also be presented.

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

12.5.2 Baseline Comparability

Not applicable.

12.5.3 Statistical Analysis

Endpoints for fixed puffing regimen will be summarized as described in section 12.1.3.

PK parameters for fixed puffing regimen will be summarized by P3P variant and analyzed using a mixed model conducted on logarithmically transformed PK parameters with fixed terms for sequence, study day, product variant, and using subject nested within sequence as random effect. Nicotine PK profiles will be summarized and plotted over time by P3P variant.

Details of model term categories for product variant and study day, accounting for multicollinearity between Day 1 and P3P 3 use, will be provided in the SAP.

Adjusted geometric least square means and ratios will be presented for the analysis of PK endpoints together with 95% confidence interval for the following effects of interest:

- P3P 2 vs P3P 3, to describe the effect of an increase of nicotine powder concentration from 2.5% to 5%
- P3P 2 vs P3P 4, to describe the effect of a decrease from 2.25 µm to 1.8 µm of the median particle size in the nicotine powder
- P3P 2 vs P3P 1, to describe the effect of flavor

12.6 Secondary Objectives and Endpoints

12.6.1 Secondary Endpoint Analysis Variables

12.6.1.1 Nicotine Exposure Parameters for *ad libitum* use

PK endpoints related to the ad libitum use period are listed in section 3.2.

Nicotine PK parameters for *ad libitum* use will be derived from plasma nicotine concentration versus time data using a NCA technique. The procedure of the baseline adjustment presented in section 12.5.1 will be used on secondary PK endpoints. In particular, the following PK parameters will be derived from nicotine levels adjusted for baseline:

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

Unadjusted Background-corrected PK parameters will also be presented.

12.6.1.2 PD endpoints for the fixed puffing regimen and *ad libitum* use

PD endpoints are listed in section 3.2.

For the VAS craving score AUC_{VAS} will be derived for each puffing regimen: $AUC_{\text{VAS fix (0-4h)}}$ and $AUC_{\text{VAS ad lib (0-4h)}}$

12.6.2 Statistical Analysis

The same approach described in section 12.5.3 will be used for the analysis of PK parameters *ad libitum* and PD endpoints. PD endpoints will be analyzed in their original scale.

12.6.2.1 PK parameters for *ad libitum* use

PK parameters for *ad libitum* use will be summarized by P3P variant and analyzed using a mixed model with fixed terms for sequence, study day, product variant, and using subject nested within sequence as random effect. Nicotine PK profiles will be summarized and plotted over time by P3P variant.

Details of model term categories for product variant and study day, accounting for multicollinearity between Day 1 and P3P 3 use, will provided in the SAP.

12.6.2.2 VAS Craving Assessments

VAS craving assessments and AUC_{VAS} scores will be summarized over time by P3P variant and by regimen. The VAS scores will be assessed using a mixed model with sequence, study day, product variant, baseline value prior to product use, and the interaction of product and time point as fixed effects and subjects as random effect including the assessment time points as repeated measurements. AUC_{VAS} scores will be analyzed using the same model as for the PK parameters, including adjustment of baseline VAS value.

Details of model term categories for product variant and study day, accounting for multicollinearity between Day 1 and P3P 3 use, will be provided in the SAP.

12.6.2.3 Questionnaires (Adapted mCEQ and SQ)

Adapted mCEQ subscale scores and SQ answers will be summarized with descriptive statistics and displayed graphically by P3P variant. The scores/answers will be analyzed using a mixed model with fixed terms for sequence, study day, product variant, and using subject nested within sequence as a random effect.

Details of model term categories for product variant and study day, accounting for multicollinearity between Day 1 and P3P 3 use, will be provided in the SAP.

12.6.2.4 Puffing Topography

HPT parameters will be summarized by P3P variant and by product use regimen with arithmetic means, arithmetic CV, and 95% CIs.

12.6.3 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 product exposure.

AE data will serve for the primary assessment of safety. Other safety variables monitored in this study include: incidence and frequency of P3P product events including malfunction/misuse; respiratory symptoms (cough assessment VAS and Likert scales); vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; clinical chemistry, hematology, and urine analysis safety panel; physical examination; concomitant medications.

All safety data will be listed and AEs will be summarized by product variant (fixed puffing regimen and *ad libitum* use periods will be combined at the product variant level). Safety measurements assessed both after fixed puffing regimen and *ad libitum* use (vital signs, ECG etc.) will be summarized per fixed puffing/*ad libitum* use regimen and product variant.

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 (with and without laboratory related AEs), AEs by severity, and laboratory AEs. Tabulations will be performed for both the number of subjects experiencing an event and the number of events.

Safety laboratory assessments are performed on Day 2 to Day 5 in the morning prior to product use (Appendix A). Any lab related AEs 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 fixed puffing/*ad libitum* use and product variant and change from baseline will be presented for laboratory parameters, ECG, respiratory symptoms, and vital signs. Shift tables will be provided for laboratory and safety ECG data.

12.6.4 Exploratory Analyses

There are no planned exploratory analyses.

12.7 Interim Analysis

Quality assured and quality controlled data of plasma nicotine concentrations will be analyzed prior to database lock and the outcome of the analysis will be received and reviewed by the Sponsor. If plasma nicotine concentrations cannot be background corrected in a sufficient number of subjects e.g., in the event that the λz (or t1/2z) cannot be reliably estimated, modelling approaches alternative to NCA may be applied including conventional compartmental analyses..

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

13.1.1 Investigator

Investigator:	[redacted], MD CROSS Research [redacted] Phone: [redacted] Fax: [redacted] E-mail: [redacted]

13.1.2 Sponsor

Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland. Phone: +41 (58) 242 2111 Fax: +41 (58) 242 2811
[redacted], PhD Clinical Scientist	Phone: [redacted] E-mail: [redacted].pmi.com
[redacted], MSc Study Statistician	Phone : [redacted] E-mail : [redacted].pmi.com
[redacted], MD Medical Safety Officer	Phone : [redacted] Email1 : [redacted] E-mail2 : [redacted].pmi.com
[redacted], MSc Clinical Study Manager	Phone : [redacted] E-mail : [redacted]pmi.com

13.1.3 Other Responsibilities

Project Management:	Cross Research SA [redacted] [redacted],

	Switzerland
Monitoring:	[redacted]
Data Management:	Cross Research SA [redacted]
Pharmacokinetic Analyses:	[redacted]
Statistical Analyses:	Cross Research SA [redacted]

All duties and responsibilities transferred by the Sponsor to the above listed CROs will be defined in the 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 B.

13.2 Study subjects' recruitment

Study participants will be recruited from the volunteers' database maintained by the CRO. This database contains a pool of volunteers that are contacted whenever necessary to enrol subjects in a new study. Before the start of the new study, the principal 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 participants 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 course of the study, the Sponsor, any authorized representatives of the Sponsor, IEC 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, IEC 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 (2) and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in section 8 of the ICH GCP Guideline (2).

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 IEC, composition of the IEC.
- 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"(23). In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IEC will be complied with as requested by local requirements.

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 course of the investigation 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, IEC, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice must be given to the Sponsor prior to any such disclosure.

According to The Federal Act on Research involving Human Beings and the Ordinance on Clinical Trials in Human Research, the study will be registered and published in a WHO primary register or clinicaltrials.gov as well as in the supplementary federal database.

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. FDA (Food and Drug Administration). Guidance for industry - Collection of race and ethnicity data in clinical trials. 2005.

2. 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: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf (Accessed on 30 Jan 2017).

3. World Medical Association (WMA). Declaration of Helsinki - Ethical principles for medical research involving human subjects. 2013; Available from: http://www.wma.net/en/30publications/10policies/b3/ (Accessed on 16 March 2017).

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

5. WHO Study Group, Ashley DL, Ayo-Yusuf OA, Boobis AR, da Costa e Silva VL, Djordjevic MV, 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.

6. Cipolla DC, Gonda I. Inhaled nicotine replacement therapy. Asian J Pharm Sci. 2015;10(6):472-80. doi: 10.1016/j.ajps.2015.07.004.

7. Teichert A, Brossard P, Felber Medlin L, Sandalic L, Franzon M, Wynn C, et al. Evaluation of nicotine pharmacokinetics and subjective effects following use of a novel nicotine delivery system. Nicotine Tob Res. Accepted article 2017.

8. Hukkanen J, Jacob P, 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005;57(1):79-115. Epub 2005/03/01. doi: 57/1/79 [pii]

10.1124/pr.57.1.3. PubMed PMID: 15734728.

9. Philip Morris Products S.A. *Unpublished on file data:* Investigator's Brochure for P3P. Edition 1. 2017.

10. National Institute for Health and Care Excellence (NICE). Tobacco: harm-reduction approaches to smoking (NICE public health guidance 45). 2013; Available from: http://www.nice.org.uk/guidance/ph45/resources/guidance-tobacco-harmreduction-approaches-to-smoking-pdf (Accessed on 11 August 2014).

11. Marchand M, Brossard P, Merdjan H, Lama N, Weitkunat R, Ludicke F. Nicotine population pharmacokinetics in healthy adult smokers: a retrospective analysis. Eur J Drug

Metab Pharmacokinet. 2017. Epub 2017/03/12. doi: 10.1007/s13318-017-0405-2. PubMed PMID: 28283988.

12. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P, 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther. 2006;79(5):480-8. Epub 2006/05/09. doi: 10.1016/j.clpt.2006.01.008. PubMed PMID: 16678549.

13. FDA (Food and Drug Administration). Food-effect bioavailability and fed bioequivalence studies. 2002.

14. American Pharmacists Association. Cytochrome P450 enzymes: substrates, inhibitors, and inducers. Drug information handbook. 23rd ed2014. p. 2316-24.

15. Raw M, Anderson P, Batra A, Dubois G, Harrington P, Hirsch A, et al. WHO Europe evidence based recommendations on the treatment of tobacco dependence. Tob Control. 2002;11(1):44-6. PubMed PMID: 11891367.

16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. Epub 2005/08/02. doi: 10.1183/09031936.05.00034805. PubMed PMID: 16055882.

17. Hu G, Cassano PA. Antioxidant nutrients and pulmonary function: the Third National Health and Nutrition Examination Survey (NHANES III). Am J Epidemiol. 2000;151(10):975-81. Epub 2000/06/15. PubMed PMID: 10853636.

18. Sajatovic M, Ramirez LF. Fagerstrom Test for Nicotine Dependence (FTND). Rating scales in mental health. 3rd ed. USA: Baltimore : Johns Hopkins University Press; 2012. p. 344-5.

19. Moyses C, Hearn A, Redfern A. Evaluation of a novel nicotine inhaler device: part 2-effect on craving and smoking urges. Nicotine Tob Res. 2015;17(1):26-33. Epub 2014/08/02. doi: 10.1093/ntr/ntu122. PubMed PMID: 25082830; PubMed Central PMCID: PMCPmc4282120.

20. Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007;32:912–23. doi: 10.1016/j.addbeh.2006.06.028.

21. Hatsukami DK, Zhang Y, O'Connor RJ, Severson HH. Subjective responses to oral tobacco products: scale validation. Nicotine Tob Res. 2013;15(7):1259-64. Epub 2012/12/15. doi: 10.1093/ntr/nts265. PubMed PMID: 23239843; PubMed Central PMCID: PMCPmc3682844.

22. Rose JE, Turner JE, Murugesan T, Behm FM, Laugesen M. Pulmonary delivery of nicotine pyruvate: sensory and pharmacokinetic characteristics. Exp Clin Psychopharmacol. 2010;18(5):385-94. doi: 10.1037/a0020834. PubMed PMID: 20939642.

23. 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).

15 APPENDICES

Appendix A – Schedule of Events

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3	Day 4	Day 5 Discharge [q]	Day 5 to 12 Safety Follow-Up [o]
Informed consent	●							
Information on the risks of smoking/advice on smoking cessation and debriefing on P3P	●	●					●	
Inclusion/exclusion criteria [a]	●	●						
P3P product demonstration	●							
Smoking history	●							
Readiness to comply to study procedures, including period of abstinence from any tobacco and nicotine containing products	●	●						
Intention to quit smoking in the next 2 months	●	●						
Demographics [b], medical history, concomitant diseases	●							
Prior medication [c]	●							
Concomitant medication	●	●	●	●	●	●	●	●
Physical examination	●	●					●	

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3	Day 4	Day 5 Discharge [q]	Day 5 to 12 Safety Follow-Up [o]
Body height, weight and related BMI	●							
Vital signs [d]	●	●	●	●	●	●	●	
ECG [e]	●	●	●	●	●	●	●	
Spirometry	●						●	
Blood and urine sample collection for hematology, clinical chemistry, urine analysis safety panel [f]	●	●		●	●	●	●	
Blood sample collection for serology	●							
Urine drug screen	●	●						
Urine cotinine screen (dip stick)	●							
Alcohol breath test	●	●						
Urine Pregnancy test (females)	●	●					●	
trans-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma [g]			●					
FTND questionnaire	●							
Enrollment		●						
P3P product test [h]		●						
Randomization [i]				●				
P3P product use. Fixed puffing in the morning with HPT followed by *ad libitum* use in the afternoon with HPT [j]			●	●	●	●		

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3	Day 4	Day 5 Discharge [q]	Day 5 to 12 Safety Follow-Up [o]
Blood sample collection for plasma nicotine [k]			●	●	●	●	●	
VAS-craving [l]			●	●	●	●		
Adapted mCEQ [m]			●	●	●	●		
Sensory Questionnaire [m]			●	●	●	●		
Cough assessment [n]		●		●	●	●	●	
AE/SAE recording [o]	●	●	●	●	●	●	●	●
Product events Malfunctions/Misuse		●	●	●	●	●		
Support during periods of smoking abstinence (as required)			●	●	●	●	●	
Weighing of P3P products [p]			●	●	●	●		

Abbreviations: Adapted mCEQ = adapted version of the modified Cigarette Evaluation Questionnaire; AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; FTND = Fagerström Test for Nicotine Dependence (revised version); HPT = Human puffing topography; SAE = Serious adverse event; SQ = Sensory questionnaire; VAS= Visual Analog Scale.

a. Prior to enrollment at Admission the following inclusion and exclusion criteria will be re-checked: Inclusion Criteria: Subject is not planning to quit smoking within 2 months, Subject is available during the study period and ready to comply with study procedures. Exclusion criteria: Subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in study, subject has a positive urine drug screen, subject uses estrogen containing medication, female subject who is pregnant or breast-feeding, female subject of childbearing potential who does not agree to use effective contraception. The following eligibility criteria will only be checked at Admission: subjects will not be included if they have 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, race.

c. 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 criteria.

d. Systolic and diastolic blood pressure, pulse rate and respiratory rate. Assessed in the morning within 60 minutes prior to fixed puffing regimen and 60 minutes ± 10 minutes after each product use period (fixed puffing regimen and *ad libitum* use).

e. On Days 1 to 4 ECG, will be performed after fixed puffing regimen and after the *ad libitum* use period.

f. Blood samples should be taken after at least 6 hours of fasting, except at Screening where non-fasting samples can be used.

g. Sample taken in the morning prior to product use.

h. During the Admission Visit after enrollment, subjects will be asked to perform a product test with the use of up to 3 products of P3P 3.

i. A subject can be randomized only after confirmation that there are no safety concerns for the subject to continue the study as judged by the Investigator. If a sufficient number of subjects are already randomized to the study sequences, any supernumerous subjects will be discontinued from the study prior to randomization.

j. Subjects will use one variant of P3P on a given study day. They will use P3P with HPT recording in the morning at a fixed puffing regimen comprising of 12 puffs in total at a rate of one inhalation every 30 seconds (± 5 seconds). In the afternoon, subjects will use P3P with HPT recording *ad libitum* for 60 minutes. Subjects will use P3P 3 at Day 1 and P3P 1, P3P 2 and P3P 4 in a randomized sequence at Days 2, 3 and 4.

k. A total of 10 blood samples will be taken for fixed puffing PK parameter estimation at Days 1 to 4. One blood samples will be taken prior to the product use ($T_{0\ fix}$) 15 minutes ± 5 minutes (T-1). Thereafter in relation to $T_{0\ fix}$, blood will be drawn at the following time points: T1 after 2 minutes ± 1 minute, T2 after 4 minutes ± 1 minute, T3 after 7 minutes ± 1 minute, T4 after 10 minutes ± 1 minute, T5 after 15 minutes ± 2 minutes, T6 after 30 minutes ± 2 minutes, T7 after 1 hour ± 5 minutes, T8 after 2 hours ± 5 minutes, and T9 after 4 hours ± 5 minutes.

   A total of 8 blood samples will be taken for the *ad libitum* PK parameter estimation at Days 1 to 4. One blood sample will be taken prior to product use ($T_{0\ ad\ lib}$) at 15 minutes ± 5 minutes (T-1). In relation to $T_{0\ ad\ lib}$, blood will be drawn at the following time points: T1 after 10 minutes ± 1 minute, T2 after 20 minutes ± 2 minutes, T3 after 30 minutes ± 2 minutes, T4 after 40 minutes ± 5 minutes and T5 after 1 hour ± 5 minutes, T6 after 2 hours ± 5 minutes, and T7 after 4 hours ± 5 minutes.

   A total of 5 blood samples will be taken at Day 5. Blood samples will be taken in relation to $T_{0\ ad\ lib}$ from the last product use at the following time points: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes, T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes and T5 after 24 hours ± 30 minutes.

l. The VAS craving will be completed by the subject at Days 1 to 4. For the fixed puffing regimen the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ fix}$, all other assessments will be done after $T_{0\ fix}$, at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. For the *ad libitum* use period the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ ad\ lib}$, all other assessments will be done after $T_{0\ ad\ lib}$, at 10 minutes ± 2 minutes, at 20 minutes ± 2 minutes, 30 minutes ± 5 minutes, 40 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each.

m. The adapted mCEQ and SQ questionnaires will be answered within 60 minutes after the end of the *ad libitum* use period.

n. VAS, three Likert scales and one open question. The cough questionnaire will be completed at Admission prior to product test and 24 hours (± 1 hour) after $T_{0\ fix}$ for each variant (but prior to next variant use).

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

p. All P3P products will be weighed before and after use.

q. All examinations listed at Discharge, with the exception of blood sampling for nicotine measurement and cough assessment, should also be conducted in subjects prematurely terminating the study (early termination procedures).

Appendix B - Participating Laboratories

Bioanalytical laboratory (Plasma Nicotine and CYP2A6 analysis):

Celerion, Inc.

[redacted]

Clinical Safety Laboratory (Hematology, Clinical Chemistry and Urine Analysis):

[redacted]

Appendix C - Laboratory Values

Table C1 Abnormal Laboratory Values Rating: Serum Chemistry Parameters

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

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
(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 [a] (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 4.03.Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, U.S. Department of Health and Human Services, FDA, Center for Biologics Evaluation and Research - Guidance for Industry.

Table C2 Abnormal Laboratory Values Rating: Hematology Parameters

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Anemia (Hemoglobin) [a] (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 threateming consequences; urgent intervention indicated
Hemoglobin increase [a] – (g/dL)	Increase in >0 – 2 above ULN or above Baseline if Baseline is above ULN	Increase in >2 – 4 above ULN or above Baseline if Baseline is above ULN	Increase in >4 above ULN or above Baseline if Baseline is above ULN	-
WBC Decrease [a] - (cell/mm^3) (10^{-9}/L)	 <LLN – 3000; <LLN – 3.0	 <3000 - 2000; <3.0 – 2.0	 <2000 - 1000; <2.0 – 1.0	 <1000; <1.0
Lymphocytes increase [a] (cell/mm^3)	 -	 >4,000 – 20,000	 >20,000	 -
Lymphocytes decrease [a] (cell/mm^3) (10^{-9}/L)	 <LLN – 800; <LLN – 0.8	 <800 - 500; <0.8 – 0.5	 <500 - 200; <0.5 – 0.2	 <200; <0.2

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Neutrophils Decrease [a] (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 [a] (cell/mm3) (10-9/l)	<LLN – 75,000; <LLN – 75.0	<75,000 – 50,000; <75.0 – 50.0	<50,000 – 25,000; <50.0 – 25.0	<25,000; <25.0

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

Data Source:

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

Table C3 Abnormal Laboratory Values Rating: Urine analysis Parameters

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

Data Source:

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

Appendix D – Human Puffing Topography Parameters

Table D1 Per-puff parameters

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

Table D2 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
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
Puffing Intensity	SMINT	TVOL/TDFi	mL/s
Puffing Time Index	PTI	(100*TDi)/TDFi	%
Puff Frequency	PFeq	NPC/(TDFi/60)	