PMI RESEARCH & DEVELOPMENT

Research Study Protocol

P3P-SE-02-RU

Study Title:	A randomized, double-blinded, 2-arm parallel groups, single center study to assess product use and adaptation, safety and tolerability of P3P, a novel nicotine-containing product, in adult healthy cigarette smokers switching to one of two P3P variants for one month.
Short Name:	Product use and adaptation, safety and tolerability of P3P in adult healthy smokers switching to it.
Registration Number:	Not assigned
Product Name:	P3P
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version Number:	Final 2.0
Date:	12 June 2019
Authors:	[redacted], PhD, Clinical Scientist [redacted], MEng, MSc, Study Statistician [redacted], MD, Medical Safety Officer

SUMMARY OF CHANGES

	Version	Date	Amendment
First updated protocol	Final Version 2.0	12 June 2019	Non-substantial amendment
Original protocol	Final Version 1.0	23 January 2019	

The following non-substantial changes were made to the original research study protocol P3P-SE-02-RU (Final Version 1.0) dated 23 January 2019 generating the updated version (Final Version 2.0) dated 12 June 2019.

Details on the protocol sections changed are provided in the table below. For identification of the changes, the previous and the amended texts are provided. The new text has been highlighted in bold (e.g. **new text**) and deleted text has been crossed out (e.g. ~~deleted text~~).

Changes from Final 1.0 to Final 2.0		
Section		**Changes**
	General	The version number and the revision date were updated. A "**Summary of changes**" section was added. Several typing errors were corrected. The list of references, abbreviations and table of contents were updated.
7.3.9	Spirometry	Old text: Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set Amended text: Spirometry predicted values will be standardized to the~~ National Health and Nutrition Examination Survey III predicted set~~ **European Community for Coal and Steel (ECCS) reference equations as published in the 1993 ERS statement** Reason to change: To correct an error in the previous version in order to use predicted sets/equations derived from European rather than American population.

7.5.1	Table 2 footnote	Old text: * Except at Screening where non-fasting glucose will be assessed Amended text: *Except at Screening where non-fasting glucose ~~will~~ **can** be assessed Reason to change: Specify that at screening collection of non-fasting samples for glucose analysis is allowed, although this is not a requirement (if subjects have been fasting, glucose samples can still be collected and analyzed).
13.1.1	Investigator	Old text: E-mail: [redacted] Amended text: E-mail: [redacted] Reason to change: To correct a typing error in the investigator's e-mail address.
Appendix C	Table C2	Old text: 10^{-9}/L Amended text: ~~10^{-9}/L~~ 10^{9}/L Reason to change: To correct a typing error in the unit for WBC, lymphocytes, neutrophils and platelets.

SYNOPSIS

Sponsor:

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

Product Name:

P3P

Study Title:

A randomized, double-blinded, 2-arm parallel groups, single center study to assess product use and adaptation, safety and tolerability of P3P, a novel nicotine-containing product, in adult healthy cigarette smokers switching to one of two P3P variants for one month.

Study Number:

P3P-SE-02-RU

Short Study Title:

Product use and adaptation, safety and tolerability of P3P in adult healthy smokers switching to it.

Objectives and Endpoints:

The goal of the proposed research study is to evaluate the adaptation of product use in adult, current cigarette smoking subjects between baseline and after 1 month of use of one of two P3P variants. The effect of P3P use behavior on nicotine pharmacokinetic (PK) profile, acceptability, as well as the safety and tolerability of P3P over a period of 1 month will be investigated. In addition, the overall use of tobacco and nicotine containing product use will be monitored.

Primary Objective and Endpoints:

1. To assess nicotine pharmacokinetics following use of a single P3P-1mg or P3P-2mg product on Day 1 and Day 30.

   Endpoints:

   - Plasma nicotine time-concentration profile from prior product use to 4 hours post start of product use;

- PK parameters: maximum plasma concentration (C_{max}); time to maximum concentration (t_{max}); Area under the concentration-time curve from start of product use to 4 hours ($AUC_{(0-4h)}$).

Secondary Objectives and Endpoints:

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

   Endpoints:

   - Visual Analogue Scale (VAS)-craving assessment in parallel with PK assessment on Day 1 and Day 30;
   - Sensory Questionnaire on Day 1 and Day 30;
   - ABOUT™-Product Experience Questionnaire on Day 1 and Day 30.

2. To assess product acceptance and puffing/inhalation behavior of both P3P variants

   Endpoints:

   - Product acceptance questionnaire on Day 1 and Day 30;
   - Puffing/inhalation behavior question:
     - Evaluated by site staff on Day 1 and Day 30
     - Answered by subject on Day 2, Day 7, Day 15, Day 22 and Day 29.

3. To assess nicotine/tobacco product use.

   Endpoints:

   - Number of P3P, cigarettes, e-cigarettes or/and other nicotine/tobacco product use from Day 1 to Day 30;
   - Change in the number of cigarettes used throughout the study as compared to the reported number at Screening.

4. To assess safety and tolerability during the study.

   Endpoints:

   - Incidence of adverse events (AEs), serious adverse events (SAEs);
   - Frequency of adverse events (AEs), serious adverse events (SAEs);
   - Incidence of P3P product events including malfunction/misuse;
   - Frequency of P3P product events including malfunction/misuse;
   - Physical examination changes from baseline;
   - Cough assessment 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 (FEV1, FEV1 % predicted, FVC, FVC % predicted, FEF 25, FEF 25 % predicted, FEF 75, FEF75 % predicted, FEF 25-75, FEF 25-75 % predicted, FEV1/FVC);
- Changes from baseline in clinical chemistry, hematology, and urinalysis safety panel;
- Concomitant medications.

5. To assess the exposure to harmful and potentially harmful constituents (HPHCs) in spot urine expressed as concentration adjusted for creatinine from Day -1 to Day 30.
   Endpoints:
   - Biomarker of exposure (BoExp) to nicotine: Nicotine equivalents (NEQ);
   - BoExp to NNK: 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL);
   - BoExp to Acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).

6. To assess tobacco and nicotine containing product dependence at Day -1 and at Day 30.
   Endpoint:
   - ABOUT™-Dependence Questionnaire.

7. To assess cytochrome P450 2A6 (CYP2A6) enzymatic activity at Day 1 and at Day 30.
   Endpoint:
   - Molar metabolic ratio of trans-3'-hydroxycotinine/cotinine in plasma.

8. To estimate the amount of powder extracted from P3P used for PK assessment.
   Endpoint:
   - Weight difference of P3P before and after use.

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.

Study Hypothesis:

The study will be descriptive in nature. However, for the ANOVA tests, the following hypothesis will be tested:
H_0: $\mu 1 = \mu 2$
H_1: $\mu 1 \neq \mu 2$
where $\mu 1$ and $\mu 2$ are the means (arithmetic or geometric) for each product variant, respectively.

Study Design:

This is a research study of P3P with daily product use of up to 15 P3P products over 1 month including 2 occasions of confinement period (3 days at V2 and 2 days at V6). From the start of the exposure period onwards, subjects will be instructed to use P3P exclusively. Subjects will be randomized to use either P3P-2mg or P3P-1mg.

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.

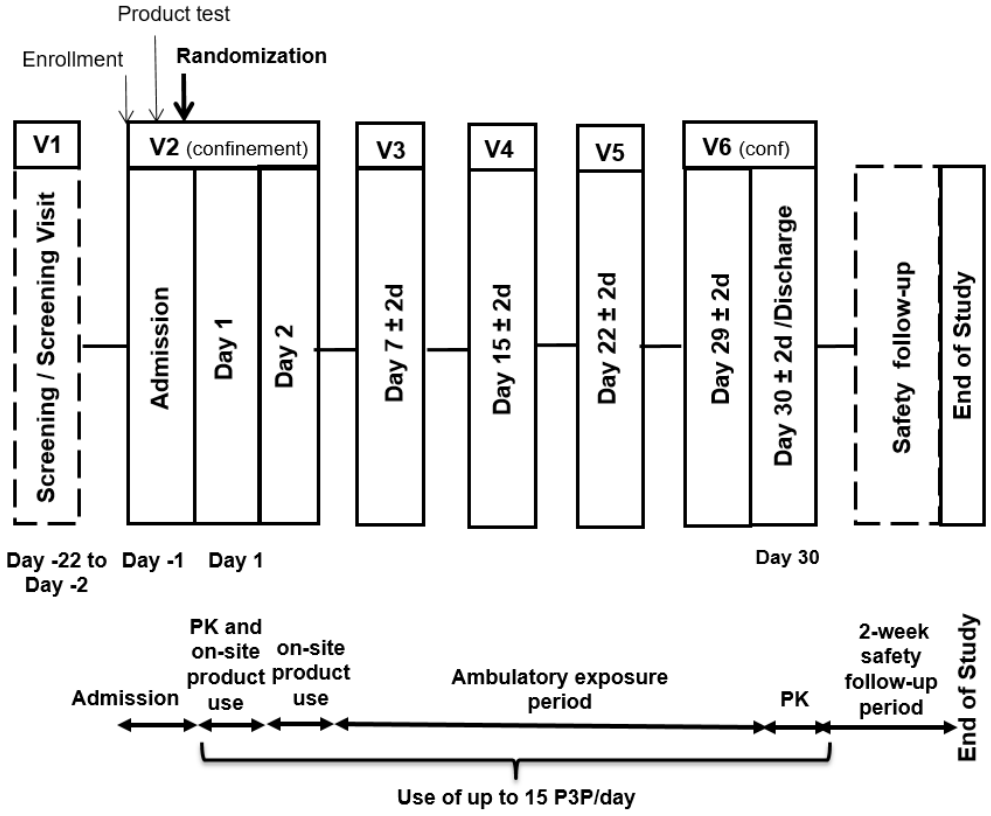

Figure 1 Study Flow Chart

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 6 P3P products (alternating between P3P-1mg and P3P-2mg). In order to continue in the study, each subject will need to test at least one product of each P3P variant during the product test. Subjects should be abstinent from the use of any tobacco/nicotine containing products for at least 4 hours prior to product test. After the product test, subjects not willing and/or not ready to use P3P will be discontinued from the study. Subjects willing and ready to use P3P during the study will be randomized either to P3P-1mg or P3P-2mg in a 1:1 ratio and will start their first overnight (confinement) period for pharmacokinetics assessments on Day 1. The subjects and the Investigator will be blinded to the randomization arm.

On Day 1, after at least 10 hour abstinence from any tobacco/nicotine containing products, subjects will use a single P3P product, as randomized, for a duration of up to 15 minutes. The start of product use will be defined as T_0.

A total of 11 blood samples will be taken for PK parameter estimation. Three blood samples will be taken prior to the product use (T_0) and 8 aditionnal blood samples will be taken at specific timepoints within 4h after the start of product use.

Pharmacodynamic effects related to craving will be assessed using a VAS scale at different time points before, during and after product use. Product evaluation using the ABOUT^{TM}-product experience questionnaire, the sensory questionnaire and the product acceptance questionnaire will be assessed after the end of product use.

Each P3P used for PK assessment will be weighted before and after product use to estimate the amount of nicotine delivered in the aerosol.

After the end of blood sampling for PK estimation, subjects will stay on-site until the evening of Day 2 and will be allowed to use up to 15 P3P products/daily during these two days. Safety assessments will be performed both on Day 1 and Day 2.

Subjects will be instructed to use exclusively P3P for the entire 1-month duration of the exposure period (from the end of V2 until discharge at V6). Use of cigarettes and/or other tobacco and nicotine containing products during the ambulatory exposure period will not be a reason for discontinuing a subject from the study, but should be avoided as much as possible. At V2, subjects will be trained on how to record their use of P3P and other tobacco/nicotine containing products in a designated website during the entire ambulatory exposure period.

Subjects will return to the investigational site for weekly visits, V3 (Day 7), V4 (Day 15), V5 (Day 22) and V6 (Day 29) with a visit time window of ± 2 days each. The visit days and windows will be calculated from Day 1. During these visits, product will be resupplied and selected safety assessments will be performed.

At V6 subjects will remain at the investigational site for their confinement period for pharmacokinetics assessments on the second day of this visit, Day 30. There will be a washout of at least 10 hours before T_0 to allow adequate background correction of the nicotine plasma concentrations. The assessments performed at Day 30 will be the same as those described for Day 1.

After discharge on Day 30 or early termination, subjects will enter a 14-day Safety Follow-Up Period during which new AE/SAEs will be collected and ongoing AEs/SAEs will be followed-up by the site. 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 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 the subject is lost to follow up. At the end of the Safety Follow-Up, all subjects will be contacted via phone in order to check the status of the ongoing AEs and also to collect any new AE/SAE experienced by the subjects. 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 until resolution, stabilization or the determination of a plausible explanation for them was found, regardless of the end of the 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 and dated the ICF and is able to understand the information provided in it.
2. Smoking male or female aged between 21 and 65 years old inclusive.
3. Subject has been a smoker for at least the last 3 years prior to the Screening Visit and has smoked 5 to 15 commercially available cigarettes per day for the last 3 months prior to Screening.
4. Subject has a positive urinary cotinine test (cotinine $\geq$ 200 ng/mL).
5. Subject does not plan to quit smoking within 2 months.
6. Smoking, healthy subject as judged by the Investigator or designee based on available assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, chest X-ray, ECG and medical history).
7. Availability for the entire study period and willingness to comply with study procedures, including intermittent dietary restrictions.
8. Ready to switch from smoking cigarettes to using P3P for the duration of the study.

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 asthma condition (post-bronchodilator FEV1/FVC < 0.75 and reversibility in FEV1 ≥ 12% and > 200 mL from pre- to post-bronchodilator values).
6. Subject has (FEV1/FVC) < 0.7 and FEV1 < 80% predicted value at post-bronchodilator spirometry.
7. Subject has a history of hypersensitivity to [redacted] or menthol.
8. Subject has a contraindication for using salbutamol and/or albuterol as per the summary of product characteristics for the given product.
9. Subject has donated or received whole blood or blood products within 3 months prior to Screening Visit.
10. Subject has a BMI < 18.5 kg/m^2 or > 32.0 kg/m^2.
11. 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.
12. Subject has a positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C.
13. Subject has a positive alcohol breath test and/or a history of alcohol disorder within the past 2 years.
14. Subject has a positive urine drug test.
15. Subject or one of their family members[a] is a current or former employee in the tobacco industry.
16. Subject or one of their family members[a] is an employee of the investigational site or of any other parties involved in the study.
17. Subject has participated in another clinical study within 3 months prior to the Screening Visit.

18. Subject has been previously screened or enrolled in this study.
19. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding.
20. For women of childbearing potential only[b]: subject does not agree to use an acceptable method of effective contraception.[c]

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

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

[c] Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-Up Period.

Investigational Products

P3P will be provided by the Sponsor. P3P is a single use product which has two components that perform different functions:

- A Consumable component, which comprises a tube-shaped body and a capsule containing the nicotine powder. Once the capsule is activated, i.e. pierced with an Accessory component, the user is able to draw on the Consumable so that airflow passes through the Consumable and releases the powder from the Capsule.
- An Accessory component, which is a mechanical unit with a needle to pierce the Capsule that enables the release of the powder from the capsule.

Two product variants (P3P-2mg and P3P-1mg) will be tested in this study. The formulations in P3P-2mg and P3P-1mg variants have already been assessed in a short-term pharmacokinetics study (ClinTrials.gov: NCT03369340).

Study Duration:

The entire study per subject will last 44 to 70 days. This will include a screening period of up to 3 weeks prior to Admission (Day -22 to Day -2), the admission day (Day -1), 30-day period of P3P use of up to 15 products per day (Day 1 to Day 30), and a 14-days Safety Follow-Up Period. The end of the study (EOS) for a subject is defined as either the Discharge at Day 30, or the date of early termination of the subject, plus the 14 days for the Safety Follow-Up Period. The end of the whole study corresponds to the individual EOS of the last subject.

Statistical Methods:

All data will be presented in listings. All endpoints will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data, arithmetic means, 95% CIs, and standard deviations, median, first and third quartiles, minimum and maximum. Change from baseline will be added to the summary statistics when applicable. For log normally distributed endpoints geometric mean, 95% CIs of the geometric mean, geometric CV will be presented instead of arithmetic mean, 95% CI, and SD and percent change from baseline will be presented instead of change from baseline. 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.

Nicotine PK parameters:

Nicotine PK parameters will be derived from plasma nicotine versus time data. $AUC_{(0\text{-}4h)}$ will be derived using the trapezoidal rule. To minimize the carry-over effect in the nicotine plasma PK parameters due to limited washout periods, background-concentration correction will be applied to the nicotine concentration data.

Baseline nicotine concentration (C_0) will be defined as the last measured concentration prior to T_0 of each visit. The baseline correction will be implemented by calculating the PK parameters using adjusted concentration values as described below (1):

- Calculate the slope using a linear regression on the log concentration of the 3 pre- T_0 timepoints.
- If the slope is <= 0, then use the slope to determine to coefficient of elimination λ_z.
- If the slope is > 0, then use the average (geometric mean) of the subject's slopes that are <= 0 from the other visits to determine the coefficient of elimination λ_z. Please note if the subject's slopes are positive for all of the visits, baseline corrected PK parameters will not be calculated.
- Adjust each concentration value post-baseline using the following formula:

$$cC_t = C_t - C_0 * e^{-\lambda zt}.$$

Unadjusted PK parameters will also be presented.

An analysis of variance (ANOVA) will be conducted for Day 1 and Day 30 on background-corrected $AUC_{(0\text{-}4h)}$ and C_{max} and geometric least square means and 95% confidence intervals for each variant and least square mean ratio and 95% confidence intervals of P3P-2mg:P3P-1mg ratio will be presented.

Sample Size:

A total of 60 subjects will be randomized with a 1:1 randomization ratio (~30 subjects randomized to P3P-1mg and ~30 to P3P-2mg). The sample size is empirically based.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

ABOUT	Assessment of behavioral outcomes related to tobacco and nicotine products
AE	Adverse event
ANOVA	Analysis of variance
$AUC_{(0\text{-}4h)}$	Area under the concentration-time curve from T_0 to 4h after T_0
BMI	Body mass index
BoExp	Biomarker of exposure
C_{max}	Maximum concentration
CEMA	2-cyanoethylmercapturic acid
CDISC	Clinical data interchange standards consortium
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events and common toxicity criteria
CTMS	Clinical trial management system
CV	Coefficient of variation
CYP2A6	Cytochrome P450 2A6
DMP	Data management plan
DVP	Data validation plan
ECG	Electrocardiogram
EOS	End of study
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
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	Elimination rate constant
MedDRA	Medical dictionary for regulatory activities
NCP	Nicotine containing product
NEQ	Nicotine equivalents
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PMPSA	Philip Morris Products S.A.
RRP	Reduced risk product
RSR	Research study report
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
T_0	Time point of start of product use
$t_{1/2z}$	Terminal elimination half-life
t_{max}	Time to maximum concentration
Total NNAL	Total 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol
[redacted]	[redacted]
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 30, or the date of early termination of the subject, plus the Safety Follow-Up Period. The end of the whole study corresponds to the individual EOS of the last subject.
Enrollment	On Admission Visit (Day -1) for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily assessed and met.
Randomization	Allocation of the respective product, P3P-1mg or P3P-2mg, after product test on Day -1.
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 Council for 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 follow the principles as defined in the ICH GCP (2), in the Declaration of Helsinki (3) and other applicable local regulation. The Investigator and any designee agree 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 included in the Investigator's study file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

Before or at the beginning of the Screening Visit, 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, time and signature of both the subject and the Investigator who conducted the informed consent discussion during Screening Visit. No study-specific procedures will be performed before the ICF has been signed.

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.

Each subject will have to consent that blood samples collected for evaluation of nicotine concentrations and CYP2A6 activity as well as urine samples collected for evaluation of biomarkers of exposure (BoExp) (i.e. NEQ, NNAL and CEMA) and creatinine will be sent abroad for analysis.

Each subject will also have to consent that blood and urine samples collected for biobanking at V2 and V6 will be sent abroad for long-term storage after having received the necessary authorization from Russian Authorities. Following completion of this study, biobanking samples will be subsequently analyzed. The analytical methods that will be applied include biomedical technology including genetic and molecular technology (metabolic, protein, lipid and RNA profiling). The subjects will be informed that the analysis of biobanking samples does not intend to diagnose any disease. Any results obtained are for research purpose only and will not be communicated to the investigator and subjects. The analyses performed will be covered by data confidentiality, as for the main analyses described in this protocol.

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 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 analyses 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 about the product is received, the Sponsor will make every effort to inform current and past study participants as appropriate.

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 continue smoking. The development of novel tobacco and nicotine containing products with the potential to present less risk of harm than cigarettes represents an approach to reduce cigarette-related deaths and diseases among smokers who would otherwise continue to smoke (5). These products aim to substantially reduce or eliminate the exposure to harmful and potentially harmful constituents (HPHCs), with the exception of nicotine, while providing acceptable substitutes for cigarettes.

Several public health agencies have advocated a potential role for such novel products in tobacco harm reduction. Public Health England stated "*The current best estimate is that e-cigarettes are around 95% less harmful than smoking*" (6) and the Royal College of Physicians has recommended "*in the interests of public health it is important to promote the use of e-cigarettes, NRT* (nicotine replacement therapy) *and other non-tobacco nicotine products as widely as possible as a substitute for smoking in the UK*" (7).

In that context, Philip Morris Products S.A. (PMPSA) is developing and scientifically substantiating Reduced-Risk Products (RRPs)[1] that have the potential to reduce individual risk and population harm in comparison to smoking cigarettes. One of these RRPs is P3P.

2.1.2 Description of the Product and Scientific Findings

P3P is a nicotine-containing product (NCP) which generates an inhalable aerosol from nicotine-containing powder when air is drawn through it with a sufficient flow rate. By design, the P3P aerosol does not contain HPHCs associated with burning/heating tobacco or with heating organic carrier compounds such as propylene glycol or glycerol usually found in liquids used in e-cigarettes.

P3P consists of a P3P body in the shape of a cigarette-sized tube which contains a capsule with the P3P powder. The capsule is pierced (activated) using a P3P piercing accessory before use. The P3P powder is composed of a nicotine-containing powder mixed with menthol flavor

[1]Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. Philip Morris Products S.A.I has a range of RRPs in various stages of development, scientific assessment and commercialization. Because Philip Morris Products S.A.'s RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

particles. The nicotine-containing powder has a particle size that allows deep lung deposition whereas the flavor particles have a larger particle size and deposit in the oropharyngeal cavity. One P3P product contains 1 or 2 mg of nicotine.

The ability to regulate smoke and nicotine intake on a puff-by-puff basis has been described to occur early in the tobacco-dependence process (8, 9). Changing a current cigarette to a novel tobacco /nicotine-containing product requires an adaptation in product use behavior as has been described, for example for low-yield cigarettes, electronic cigarettes (e-cigarettes) or a novel Tobacco Heating System (10-15). Initial studies with e-cigarettes showed low nicotine absorption in smokers (16). Improvements in e-cigarette devices including power settings allowed faster and more efficient delivery of nicotine to the users (17). Experienced users of e-cigarettes have a high variability in their use behavior reflecting the large variety of e-cigarette devices, e-liquid nicotine concentrations and flavors (18-20).

It is expected that subjects in this study will need to adapt their product use behavior to P3P to achieve nicotine absorption comparable to smoking cigarettes: P3P does not require heating or electronics in its operation, the generation of nicotine-aerosol from nicotine-containing powder requires a flow rate that is higher than what has been observed in cigarette smokers (12, 21).

Non-clinical information on P3P to support this clinical study is presented in the Investigator's brochure (IB) (22).

One pharmacokinetic clinical study was conducted with P3P in 19 smokers in Switzerland (ClinTrials.gov: NCT03369340). In this study, following a single use of four P3P variants, nicotine C_{max} was 1.1 ng/mL for the 1 mg variant and between 2.1 and 3.1 ng/mL for the 2 mg variants and was reached after 15-22.5 minutes (T_{max}). C_{max} values for P3P were lower compared to literature-reported C_{max} for cigarettes which ranges between 10-30 ng/mL (23-25) or Nicorette® Inhalator, a nicotine replacement therapy, for which C_{max} values of 6-8 ng/mL have been described (25, 26). T_{max} was at a later timepoint for P3P compared to cigarettes for which maximal plasma concentration is reached after 5-8 minutes, but earlier compared to Nicorette® Inhalator for which T_{max} is at 30 minutes. Thus, the observed concentration-time profile for P3P is indicative of a partial pulmonary and partial oromucosal absorption compared to the pulmonary absorption for cigarettes and the oromucosal absorption of Nicorette® inhalator. The adaptation of the product use behavior in these subjects, which were unfamiliar with P3P may have been incomplete. The product was generally well tolerated and no safety concern was revealed.

2.2 Purpose of the Study

The purpose of the study is to evaluate the adaptation of product use in adult, current cigarette smoking subjects between baseline and after 1 month of use of one of two P3P variants.

The effect of P3P use behavior on nicotine pharmacokinetic (PK) profile, acceptability, as well as the safety and tolerability of P3P over a period of 1 month will be investigated. In addition, the overall use of tobacco and nicotine containing products will be monitored.

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.

Any subject who is motivated to quit smoking during the study will be given the opportunity to continue his/her smoking cessation attempt and will be referred to appropriate medical services for continuing support and counselling at a higher level. The subject will not be discontinued from the study, will come to all scheduled visits during which all safety assessments will be performed, and his/her financial compensation will not be affected. Subjects who decide to quit using tobacco and nicotine containing products will not be provided with P3P anymore.

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

- Risks related to blood sampling (*e.g.*, excessive bleeding, fainting, hematoma, paresthesia or infection).
- Risks related to chest X-ray (*e.g.*, a small increase of risk to develop cancer later in life).
- Risk related to spirometry testing procedures (*e.g.*, dizziness or fainting).

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 (27), 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 expected 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.

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 (headache, dizziness, tremor, blunting of emotions, and decreased ability to concentrate), gastrointestinal system (nausea, hyper-salivation, abdominal pain, vomiting, diarrhea) or

respiratory system (cough, increase bronchial secretions, shortness of breath). 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.

All risks related to study procedures or IP will be explained in detail to the subject. 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 assessment of all study subjects with follow-up of those who have experienced 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 assess nicotine pharmacokinetics following use of a single P3P-1mg or P3P-2mg product on Day 1 and Day 30.

   Endpoints:

   - Plasma nicotine time-concentration profile from prior product use to 4 hours post start of product use;
   - PK parameters: maximum plasma concentration (C_{max}); time to maximum concentration (t_{max}); Area under the concentration-time curve from start of product use to 4 hours ($AUC_{(0-4h)}$).

3.2 Secondary Objectives and Endpoints

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

   Endpoints:

   - Visual Analogue Scale (VAS)-craving assessment in parallel with PK assessment on Day 1 and Day 30;
   - Sensory Questionnaire on Day 1 and Day 30;
   - ABOUT^{TM}-Product Experience Questionnaire on Day 1 and Day 30.

2. To assess product acceptance and puffing/inhalation behavior of both P3P variants

   Endpoints:

   - Product acceptance questionnaire on Day 1 and Day 30;
   - Puffing/inhalation behavior question:
     - Evaluated by site staff on Day 1 and Day 30
     - Answered by subject on Day 2, Day 7, Day 15, Day 22 and Day 29.

3. To assess nicotine/tobacco product use.

   Endpoints:

   - Number of P3P, cigarettes, e-cigarettes or/and other nicotine/tobacco product use from Day 1 to Day 30;
   - Change in the number of cigarettes used throughout the study as compared to the reported number at Screening.

4. To assess safety and tolerability during the study.
   Endpoints:
   - Incidence of adverse events (AEs), serious adverse events (SAEs);
   - Frequency of adverse events (AEs), serious adverse events (SAEs);
   - Incidence of P3P product events including malfunction/misuse;
   - Frequency of P3P product events including malfunction/misuse;
   - Physical examination changes from baseline;
   - Cough assessment 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 (FEV1, FEV1 % predicted, FVC, FVC % predicted, FEF 25, FEF 25 % predicted, FEF 75, FEF75 % predicted, FEF 25-75, FEF 25-75 % predicted, FEV1/FVC);
   - Changes from baseline in clinical chemistry, hematology, and urinalysis safety panel;
   - Concomitant medications.

5. To assess the exposure to harmful and potentially harmful constituents (HPHCs) in spot urine expressed as concentration adjusted for creatinine from Day -1 to Day 30.
   Endpoints:
   - Biomarker of exposure (BoExp) to nicotine: Nicotine equivalents (NEQ);
   - BoExp to NNK: 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL);
   - BoExp to Acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).

6. To assess tobacco and nicotine containing product dependence at Day -1 and at Day 30.
   Endpoint:
   - ABOUT^{TM}-Dependence Questionnaire.

7. To assess cytochrome P450 2A6 (CYP2A6) enzymatic activity at Day 1 and at Day 30.
   Endpoint:
   - Molar metabolic ratio of trans-3'-hydroxycotinine/cotinine in plasma.

8. To estimate the amount of powder extracted from P3P used for PK assessment.
   Endpoint:
   - Weight difference of P3P before and after use.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blinded, 2-arm parallel groups, single-center study conducted in current adult smokers willing to switch from smoking cigarettes to using P3P for 1 month. P3P product use will be of up to 15 products per day over 1 month and the study will include 2 occasions of confinement period (3 days at V2 and 2 days at V6). From the start of the exposure period onwards, subjects will be instructed to use P3P exclusively. Subjects will be randomized to use either P3P-2mg or P3P-1mg.

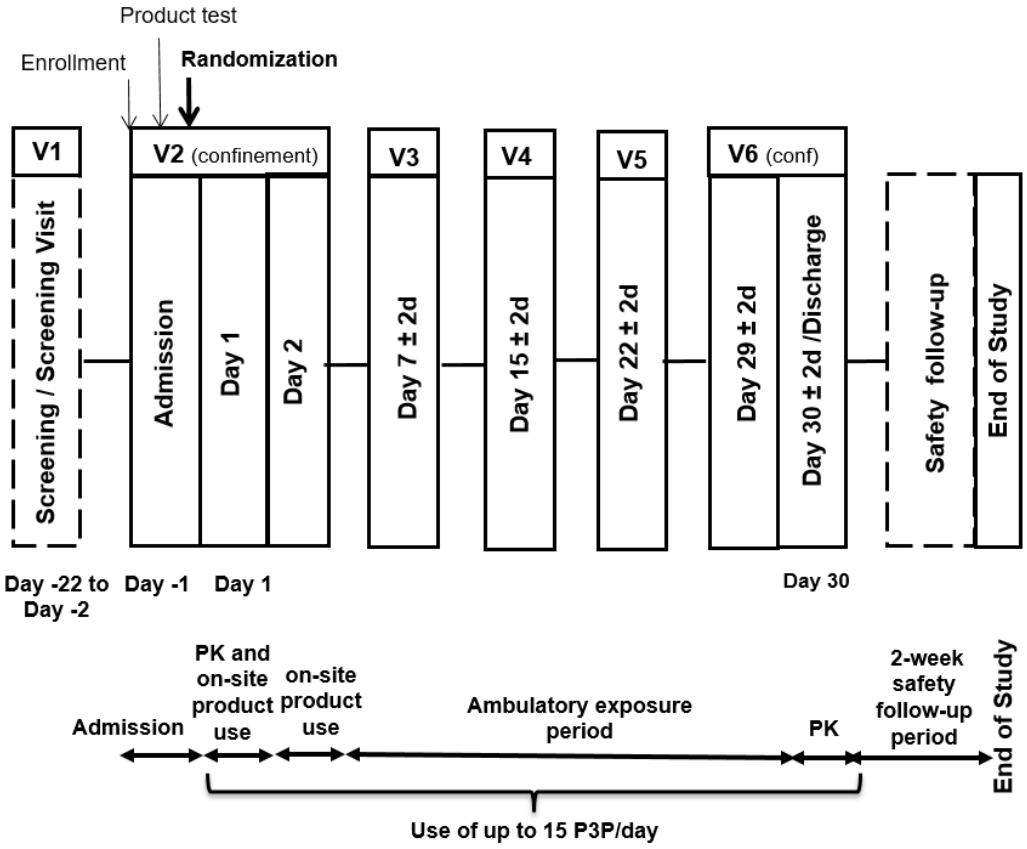

Figure 2 Study Flow Chart

The Screening Visit (V1 [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 (V2 [Day -1])

At V2, 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 and will undergo baseline assessments. All subjects that are not enrolled will be considered as screen failures. At Admission, enrolled subjects will perform a product test using up to 6 P3P products (alternating between P3P-1mg and P3P-2mg). In order to continue in the study, each subject will need to test at least one product of each P3P variant during the product test. Subjects should be abstinent from the use of any tobacco/nicotine containing products for at least 4 hours prior to product test. After the product test, subjects not willing and/or not ready to use P3P will be discontinued from the study and will undertake early termination procedures on the same day (section 9.5) and will enter the 14-day Safety Follow-Up Period. Subjects willing and ready to use P3P during the study will be randomized either to P3P-1mg or P3P-2mg in a 1:1 ratio and will start their first overnight (confinement) period for pharmacokinetics assessments on Day 1. The subjects and the Investigator will be blinded to the randomization arm.

The Exposure Period (V2 [Day 1] to discharge at V6 [Day 30])

On Day 1, after at least 10 hour abstinence from any tobacco/nicotine containing products, subjects will use a single P3P product, as randomized, for a duration of up to 15 minutes. The start of product use (first puff taken) will be defined as T_0.

A total of 11 blood samples will be taken for PK parameter estimation. Three blood sample will be taken prior to the product use (T_0): 1 hour ± 5 minutes, 30 minutes ± 5 minutes and 5 minutes ± 2 minutes before T_0. Thereafter in relation to T_0, blood will be drawn at the following time points: after 4 minutes ± 1 minute, after 7 minutes ± 1 minute, after 10 minutes ± 1 minute, after 15 minutes ± 2 minutes, after 30 minutes ± 2 minutes, after 1 hour ± 5 minutes, after 2 hours ± 5 minutes and after 4 hours ± 5 minutes.

Pharmacodynamic effects related to craving will be assessed using a VAS scale at different time points. The first assessment will be done 10 minutes ± 2 minutes prior to T_0, all other assessments will be done after T_0, at 4 minutes ± 2 minutes, 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 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 using the ABOUT™-Product experience questionnaire, the sensory questionnaire and the product acceptance questionnaire will be assessed after the end of product use.

Each P3P used for PK assessment will be weighed before and after product use to estimate the amount of powder/nicotine extracted from the product.

After the end of blood sampling for PK estimation, subjects will stay on-site until the evening of Day 2 and will be allowed to use up to 15 P3P products/daily during these two days. Safety assessments will be performed both on Day 1 and Day 2.

Subjects will be instructed to use exclusively P3P for the entire 1-month duration of the exposure period (from the end of V2 until discharge at V6). Use of cigarettes and/or other tobacco and nicotine containing products during the ambulatory exposure period will not be a reason for discontinuing a subject from the study, but should be avoided as much as possible. At V2, subjects will be trained on how to record their use of P3P and other tobacco/nicotine containing products in a designated website during the entire period of the study.

Subjects will return to the investigational site for weekly visits V3 (Day 7), V4 (Day 15), V5 (Day 22) and V6 (Day 29) with a visit time window of ± 2 days each. The visit days and windows will be calculated from Day 1. During these visits product will be resupplied and selected safety assessments will be performed.

At V6 subjects will remain at the investigational site for their confinement period for pharmacokinetics assessments on the second day of this visit, Day 30. There will be a washout period from any nicotine/tobacco containing products of at least 10 hours before T_0 to allow adequate background correction of the nicotine plasma concentrations. The assessments performed at Day 30 will be the same as those described for Day 1.

The Safety Follow-Up Period (from Discharge or Early Termination plus 14 days)

After discharge on Day 30 or early termination, subjects will enter a 14-day Safety Follow-Up Period during which new AE/SAEs will be collected and ongoing AEs/SAEs will be followed-up by the site. At the end of the Safety Follow-Up all subjects will be contacted via phone in order to check the status of the ongoing AEs and also to collect any new AEs experienced by the subjects. Subjects should be contacted 14-days after Day 30. In case they cannot be reached two additional attempts at the next 2 consecutive days will be made. If the subjects cannot be reached after the three attempts they will be declared lost to follow-up. Phone calls should be recorded in the source documents. Any non-serious AE that is ongoing at the time of discharge or early discontinuation or previously reported during the Safety Follow-Up will be followed-up by the Investigator or designee during 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 the subject is 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 until resolution, stabilization or the determination of a plausible explanation for them was found, regardless of the end of the 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 Russia which is 18 years old and to account for the 3 years of smoking history.

In a previous study conducted with P3P (ClinTrials.gov: NCT03369340), the pharmacokinetic profiles of nicotine following a single use of P3P were indicative of a partial pulmonary and partial oromucosal absorption with lower plasma nicotine levels compared to published data for single cigarette smoking (23, 24). It is well established that changing a current cigarette to a novel tobacco /nicotine-containing product requires an adaptation in product use behavior as has been described for low-yield cigarettes, e-cigarettes or a novel Tobacco Heating System (10-15). The changes in product use behaviour over time (e.g. potential changes in puffing/inhalation process) may result in changes in the nicotine PK profiles in particular in the absorption phase. For this reason, nicotine PK profiles and parameters following a single product use will be assessed at the beginning of the exposure period (Day 1) and at the end of the exposure period following adaptation to product use (Day 30). Sampling timepoints for determination of nicotine concentrations were selected to ensure reliable estimation of PK parameters.

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 (28). 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 before the start of product use for PK assessment to ensure appropriate washout of nicotine. Background-concentration correction will be applied to adjust for any residual carry-over effects as detailed in section 12.5.1.

In addition to the nicotine PK assessment in plasma, exposure to nicotine during the ambulatory exposure period will be assessed by measuring urinary concentrations of nicotine equivalents (NEQ) in spot urine adjusted for creatinine. During cigarette smoking, on average 98% of the nicotine dose can be accounted for in the urine. NEQ, which is the molar sum of nicotine and five of it's phase I and phase II metabolites in urine, represents more than 90% of the total dose recovered in urine (29).

Biomarkers of exposure to HPHCs found in tobacco and cigarette smoke will be measured during the study to detect reduction in the levels of these BoExp. Changes in levels of the tobacco-specific BoExp, total NNAL (30), and the BoExp to acrylonitrile, CEMA (31) which are predominantly formed during combustion of tobacco will be measured in spot urine adjusted for creatinine. Adjustment for creatinine will be performed to normalize for volume of urine excretion. As P3P is a nicotine containing product and the aerosol generated by P3P does not generate by design HPHCs other than nicotine, the levels of CEMA and total NNAL may be further used to detect cigarette use in addition to P3P use during the ambulatory exposure period and used as a chemical verification of the self-reporting.

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 (25).

4.3 Appropriateness of Measurements

All bioanalytical assays and laboratory assessments performed in the study will be carried out using appropriate and validated methods. Questionnaires used in this study, except product acceptance, craving VAS and cough assessment questionnaires, are available as validated/previously published or adapted versions of validated questionnaires. Of note, questionnaires used to assess global dependence and product experience are part of the ABOUT™ (Assessment of Behavioral OUtcomes related to Tobacco and nicotine products) Toolbox, an initiative resulting from a collaborative effort to develop fit-for-purpose measurement instruments (i.e., concept-driven instruments providing interpretable outcomes for the purpose intended) to enhance the scientific framework of harm reduction (32).

4.4 Study Duration

The entire study per subject will last 44 to 70 days. This will include a screening period of up to 3 weeks prior to Admission (Day -22 to Day -2), the admission day, 30-day period of P3P use of up to 15 products per day (Day 1 to Day 30), and a 14-days Safety Follow-Up Period. The end of the study (EOS) for a subject is defined as either the Discharge at Day 30, or the date of early termination of the subject, plus the 14 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

Sixty female or male healthy adult subjects who have smoked between 5 and 15 cigarettes per day for the last 3 months prior to Screening will be randomized in this study. Each randomization group (P3P-1mg, P3P-2mg) will be stratified on sex distribution to ensure that at least 40% of each sex is randomized in each exposure group.

5.1.1 Inclusion Criteria

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

Inclusion Criteria	Rationale	Screening	Admission (Day -1)
1. Subject has signed and dated the ICF and is able to understand the information provided in it.	Administrative	X	
2. Subject is male or female aged between 21 and 65 years old inclusive.	Safety	X	
3. Subject has been a smoker for at least the last 3 years prior to the Screening visit and has smoked 5 to 15 commercially available cigarettes per day over the last 3 months prior to Screening.	Effect	X	
4. Subject has a positive urinary cotinine test (cotinine ≥ 200 ng/mL).	Effect	X	X
5. Subject does not plan to quit smoking in the next 2 months.	Safety	X	X
6. Smoking, healthy subject as judged by the Investigator or designee based on available assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, chest X-ray, ECG and medical history).	Safety	X	
7. Availability for the entire study period and willingness to comply with study procedures, including intermittent dietary restrictions.	Effect	X	X
8. Ready to switch from smoking cigarettes to using P3P for the duration of the study.	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	Admission (Day -1)
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).	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 medical condition (including safety laboratory as per CTCAE), which as per the judgment of the Investigator would jeopardize the safety of the subject.	Safety	X	
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 asthma condition (post-bronchodilator $FEV_1/FVC < 0.75$ and reversibility in $FEV_1 \geq 12\%$ and > 200 mL from pre- to post-bronchodilator values).	Safety	X	
6. Subject has $(FEV_1/FVC) < 0.7$ and $FEV_1 < 80\%$ predicted value at post-bronchodilator spirometry.	Safety	X	
7. Subject has a history of hypersensitivity to [redacted] or menthol.	Safety	X	

Exclusion Criteria	Rationale	Screening	Admission (Day -1)
8. Subject has a contraindication for using salbutamol and/or albuterol as per the summary of product characteristics for the given product	Safety	X	
9. Subject has donated or received whole blood or blood products within 3 months prior to Screening Visit.	Safety	X	
10. BMI < 18.5 kg/m^2 or ≥ 32.0 kg/m^2.	Safety	X	
11. 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
12. Subject has a positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C.	Safety	X	
13. The subject has a positive alcohol breath test and/or had a history of alcohol disorder within the past 2 years.	Administrative	X	X
14. The subject has a positive urine drug test.	Administrative	X	X
15. Subject or one of their family members[a] is a current or former employee of the tobacco industry.	Administrative	X	
16. Subject or one of their family members[a] is employee of the investigational site or of any other parties involved in the study.	Administrative	X	
17. The Subject has participated in another clinical study within 3 months prior to the Screening Visit.	Safety	X	
18. Subject has been previously screened or enrolled in this study.	Administrative	X	
19. Subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding.	Safety	X	X

Exclusion Criteria	Rationale	Screening	Admission (Day -1)
20. For women of childbearing potential only[b]: subject does not agree to use an acceptable method of effective contraception.[c]	Safety	X	

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

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

c. Intrauterine device, intrauterine system, barrier methods of contraception (condoms, occlusive caps) with spermicidal foam/gel/film/suppository, hormonal contraception, vasectomized partner(s), or true abstinence (periodic abstinence and withdrawal are not effective methods) from Screening until the end of the Safety Follow-Up Period.

5.2 Discontinuation of Subjects from the Study

Discontinued subjects will include both subjects who withdraw from the study (subject's decision) 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. The samples collected prior to withdrawal will be analyzed, even after his/her withdrawal unless the subject confirms his/her disagreement to the site staff and the disagreement is documented.

When a subject is discontinued from the study, all early termination procedures (section 9.5) 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. Early termination visit should be performed within 7 days from the date of discontinuation. After the date of termination, the subject will enter into the 14-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. In such a situation, the subject will be discontinued immediately after the product test.

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

- Non-compliance with the study procedures based on the judgment of the Investigator.

Use of any tobacco and nicotine containing product other than P3P during the ambulatory exposure period will not lead to the discontinuation of the subject from the study. However, the subjects will be instructed to use exclusively P3P (up to 15 products daily) during this period. 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 (at least three attempts on three different days) 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 (70 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 will be considered as screen failures and will be replaced by other subjects. Re-screening of subjects will not be permitted.

Any violation of selection criteria detected after enrollment have to be reported within 24 hours after awareness to the Clinical Research Associate (Monitor).

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

6.1.1 Investigational Products

P3P is a novel type of nicotine-containing product (NCP) which generates an inhalable aerosol from nicotine-containing powder when air is drawn through it. P3P does not contain tobacco and does not require heating and/or electronics for its operation.

It is a single use product which has two components that perform different functions:

- A consumable component, which comprises a tube-shaped body and a capsule containing the P3P powder. Once the capsule is activated, i.e. pierced with an accessory component, the user is able to draw on the consumable so that airflow passes through the consumable and releases the powder from the capsule.
- An accessory component, which is a mechanical unit with a needle to pierce the capsule that enables the release of the powder from the capsule. Each capsule should be pierced immediately before product use.

The P3P powder is composed of a nicotine-containing powder mixed with menthol flavor particles. The nicotine-containing powder has a particle size that allows deep lung deposition whereas the flavor particles have a larger particle size and deposit in the oropharyngeal cavity. One P3P product contains 1 (P3P-1mg) or 2 mg (P3P-2mg) of nicotine.

P3P will be provided by the Sponsor and its distribution by site will be controlled by a qualified and appropriately trained designee as specified in the IP handling manual.

6.1.2 Packaging and Labeling

Five P3P consumables will be packed in a pouch. Four pouches (or 20 Consumables) and one accessory will be packed in a pack. Six packs will be packed in a carton. Each carton/pack/pouch will be labelled with the necessary information according to local regulatory requirements, and blinding requirements. The contents of each label will be specified in the IP handling manual.

6.2 Use of Investigational Products

Subjects can use up to 15 P3P products daily during the exposure period, except during the PK assessments and wash-out hours preceeding those assessments, as described below. 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 – V2)

After enrollment, subjects will be required to perform product test by using up to 6 P3P products (alternating between P3P-1mg and P3P-2mg). In order to continue in the study, each subject will need to test at least one product of each P3P variant during the product test. Product test must be performed after the subjects have abstained from the use of any tobacco/nicotine containing products for at least 4 hours (4h wash-out period prior to product test). The product test period should be organized in a dedicated supervised area (i.e. not a dedicated cigarette smoking area). Subjects will be instructed on how to activate and use P3Pas specified in the P3P user guide. . 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. Product test should end at least 10 hours prior to the start of product use for PK assessment on Day 1 (section 6.2.2)

After the product test, subjects not willing and/or unable to use P3P will be discontinued from the study and will enter a 14-day Safety Follow-Up Period.

At Day -1, after check-in on site, subjects will not be allowed to smoke cigarettes and/or use any other tobacco/nicotine containing products with the exception of P3P which can only be used during the product test period.

6.2.2 Product use during confinement (V2, V6)

During the investigational period subjects will be requested to attend two on-site visits with overnight stays (with a confinement of 3-days at V2 and 2-days at V6). At the beginning of these visits, subjects will be asked to give their cigarettes and used/unused P3P products to the site staff.

Smoking cigarettes and/or use any tobacco/nicotine containing products other than P3P will not be allowed on site during the visits. On the first day of V6 (Day 29), subjects will be allowed to use P3P until the evening which will be subsequently followed by a wash-out period of at least 10 hours prior to the PK assessments which will be done on the second day of the visits. P3P use on the first day of V2 will only be allowed during the product test period (section 6.2.1). P3P will be dispensed by the site staff on a product by product basis during the timeframe allowed by the protocol. The distribution should be recorded at site logs by site staff and the use of any product during the confinement days should be also recorded in the product use diary which is completed by the subject. The time of the use of the last tobacco/nicotine containing product, prior to the start of the wash-out period should be recorded.

In the morning of the second day of V2 (Day 1) and V6 (Day 30), following at least 10 hours of abstinence from any tobacco and nicotine containing products, subjects will use a single P3P product with no restrictions on the number of puffs or puffing frequency (*ad libitum* use) for a duration of up to 15 minutes. The start of product use (first puff) will be considered as T_0. The start and stop time of product use will be recorded. At V2 (Day 1), after the end of the blood sampling for PK assessments (4h after T_0) subjects will be allowed to restart the use of

P3P. Subjects will remain on-site until the evening of Day 2 and will be allowed to use up to 15 P3P products/day on Day 1 and Day 2. During this time, subjects will not be allowed to smoke cigarettes and/or use any other tobacco/nicotine containing products with the exception of P3P.

6.2.3 Ambulatory Exposure Period (Discharge at V2 until start of V6)

Subjects will be instructed to use P3P exclusively (using up to 15 products daily) from discharge at V2 until check-in at V6. Use of cigarettes and/or other tobacco and nicotine containing products during the ambulatory Exposure Period will not be a reason for discontinuing a subject from the study, but should be avoided as much as possible. During the entire exposure period, subjects will report their daily consumption in a product use diary (section 7.8.1)

6.2.4 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.

6.2.5 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 other reasons at the discretion of the Investigator. Signs suggesting respiratory disturbance (e.g., wheezing, dyspnoea, chest tightness) which may be related to P3P powder inhalation could also be taken in consideration for P3P reduced use or P3P stopping.

6.2.6 Stopping Rules for the Study

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

- are assessed as causally related to P3P
- are not considered to be consistent with continuation of the study
- are not consistent with the information provided in Section 6.5 of the current P3P Investigator's Brochure.

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

The Investigator should notify the EC in writing of the study's completion or early termination. In the event that the study is terminated early, every effort should be made by the Investigator, investigational site personnel, and Sponsor to follow AEs and SAEs for all subjects until the end of the 14-Day Safety Follow-Up Period.

6.3 Method for Assigning Subjects to Product Variant

At Day -1 after product test subjects who confirmed their willingness to continue in the study will be randomized using an interactive web response system (IWRS). Subjects will be randomized to one of the two arms: P3P-1mg or P3P-2mg in a 1:1 ratio.

Each randomization group (P3P-1mg, P3P-2mg) will be stratified on sex distribution to ensure that at least 40% of each sex is randomized in each group.

6.4 Blinding

This is a double-blinded study. Neither the site staff (except designated unblinded site staff if applicable) nor the subject will be informed about the product variant the subjects have been randomized to. PMPSA and CRO personnel will not be blinded to the randomization arm. Blinding process will be described in more details in the IP handling manual.

6.5 Investigational Product Accountability and Compliance

6.5.1 Dispensing Investigational Products

Product test at the investigational site: Product test will be performed using up to 6 P3P products(alternating between P3P-1mg and P3P-2mg). In order to continue in the study, each subject will need to test at least one product of each P3P variant during the product test. Distribution of the P3P product will be done by site staff on a product by product basis for each use. The distribution should be recorded at site logs by site staff. Used P3P consumables will be returned to the site staff at the end of each use.

Products for PK assessment and on-site use during confinement: The single P3P products used for PK assessment (second day of V2 and V6) will be provided to the subject by the site staff shortly before product use, after the product has been weighed, and will be returned to the site staff immediately after use, for after-use weighing (section 7.8.2). The products used for PK assessment will be activated (pierced) by the site staff immediately before product use.

All other products used during the confinement period will be dispensed by site staff on a product by product bases during the timeframe allowed by the protocol and will be activated by the subjects themselves.

Products for ambulatory exposure period: Starting from V2, prior to the Check-out of each visit, subjects will be provided with a sufficient number of P3P packs to cover their needs until the next visit. In the situation in which site staff judges that a re-supply is needed, optional

extra visits may be accommodated. At the visits during the ambulatory period, subjects will be asked to return all used and unused P3P packs and consumables. At V6, unused products should be returned at the beginning of the visit.

6.5.2 Storage and Accountability

The Investigator or designee will be responsible for the storage and accountability of P3P on site, in accordance with the Sponsor's requirements. The subject should be instructed to follow the storage and handling requirements of P3P as specified in the User guide.

The P3P components will be stored in a secured storage place at the investigational site with access limited to the authorized personnel only and according to the blinding requirements specified in the IP handling manual. Full accountability of the distributed products will be ensured by recording the timing and quantities of distributed products at each visit in appropriate logs by the designated site staff. Products used for product test, products dispensed during V2 and V6 and products used for PK will also be registered in an appropriate log.

6.5.3 Investigational Products Retention

Used and unused P3P products remaining on site will be destroyed or returned to the Sponsor upon study completion and as agreed with the Sponsor.

6.5.4 Compliance to Investigational Products

From Check-out at V2 until Discharge at V6, P3P product use compliance will be based on the daily self-reporting by the subjects in the product use diary (section 7.8.1). BoExp (Total NNAL and CEMA) may be used as additional tools for verifying cigarette smoking in addition to P3P use during analyses.

6.6 Restrictions

6.6.1 Smoking and Product Use 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). At Day -1 of V2, after check-in on site, smoking cigarettes and/or use any other tobacco/nicotine containing products will not be allowed. P3P use will be allowed only during the product test period.

From Day 1 until the end of the exposure period (Day 30) subjects will be instructed to exclusively use P3P. During the ambulatory visits, P3P use will be allowed except during procedures and at the discretion of the investigational site. In general, the performance of scheduled procedures has priority over the wish of a subject to use P3P. Use of cigarettes will not be allowed on site during the study visits.

An abstinence period from any tobacco/nicotine containing products of at least 10 hours must be respected before product use for PK assessment at Day 1 and Day 30 and during the blood sampling for nicotine measurement.

During the overnight on-site visits (V2 and V6) P3P will be dispensed by the site staff on a product by product basis during the timeframe allowed by the protocol. Dispensing will be recorded in an appropriate log (section 6.5)

6.6.2 Dietary Restrictions

During the overnight on-site visits: V2 and V6, 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) (33)." 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. During these visits, consumption of water is allowed as desired. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed. Subjects should be instructed to refrain from ingesting foods or beverages containing grapefruit or seville-type (bitter) oranges and marmalade within 7 days prior to the PK assessment days (Day 1 and Day 30). The same menu and meal schedule will be administered uniformly for all subjects.

There will be no dietary restrictions during the ambulatory exposure period.

Fasting state has to be observed for at least 6 hours prior to safety laboratory and biobanking blood draws at V2, V4 (safety laboratory only) and V6.

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. No concomitant medication should be taken by the subjects from Screening until the end of the ambulatory exposure period without informing the Investigator or designee.

CYP2A6 is involved in nicotine metabolism. To be eligible for the study any medication with impact on CYP2A6 metabolism including, but not limited to medication listed in Table 1, 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, any medication with impact on CYP2A6 activity must be avoided at least 14 days prior to the PK assessment at Day 1 and Day 30 or for at least 5 half-lives of the drug (whichever is longer). 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 1 CYP2A6: Substrates, Inhibitors, and Inducers (34)

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/anticonvulsants
Rifampin	Antimycobacterials
Secobarbital	Barbiturates
Substrate	**Drug Class**
Dexmedetomidine	α_2-Adrenoceptor, sedative
Ifosfamide	Anti-cancer, alkylating agents

Use of any other concomitant medication will be evaluated on a case by case basis by the Investigator. The Investigator is responsible for the medical care including medication of the subjects during their participation in the study. Any decisions regarding the prescription of medications will be made in the best interest of the subject. Any concomitant medications used will be fully documented (for details see section 7.3.4).

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 V1, V2 and V6 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 (35). 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 designee or may be given in a group session.

7.3 Clinical Assessments

7.3.1 Demographic Data

Sex, date of birth and race will be recorded for each subject at V1.

7.3.2 Tobacco and Nicotine Containing Products Use History and Habits

At V1, subjects will answer questions about their tobacco and nicotine containing products use history and habits. This self-reported daily consumption of cigarettes at V1 will be reviewed by the Investigator and used to assess eligibility for the study.

At V1 and V2 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 and the answer should be documented on source documents. Only subjects not planning to quit will be considered for participation in the study.

Furthermore, subjects will be asked if they are ready to switch from cigarette smoking to use of P3P for the duration of the study. Only subjects prepared and able to comply with this requirement will be considered for participation in the study.

7.3.3 P3P demonstration and P3P Test

All subjects will have a demonstration of P3P (without product use) at V1.

At V2, after enrollment, and after at least 4h of abstinece from the use of any tobacco/nicotine containing products, subjects will be required to perform a product test using up to 6 P3P products (alternating between P3P-1mg and P3P-2mg). Each subject will need to test at least one product of each P3P variant during the product test. They will be instructed to use the product as described in section 6.2.1.

After the product test, subjects not willing and/or unable to use P3P will be discontinued from the study and will enter a 14-day Safety Follow-Up Period.

7.3.4 Medical History, Concomitant Disease, Previous and Concomitant Medications

Relevant medical history and any concomitant disease will be documented at V1. Medical history is defined as any condition that started and ended prior to the ICF signature at V1. A concomitant disease is defined as any condition that is either detected or is still ongoing at the time of ICF signature. The final status of any concomitant disease (i.e stop date or ongoing) should be verified at each visit.

Any medication taken within 4 weeks prior to V1 and any concomitant medication will be documented. Any medication started prior to V1 and still being taken by the subject will be considered concomitant medication. Medication initiated after V1 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.

7.3.5 Physical Examination

Physical examination will be conducted at V1, V2 (at admission and prior to discharge) and V3-V6.

A full physical examination will include review of general appearance, skin, head, eyes, ears, nose and throat, thyroid gland, chest, lungs, back, abdomen, dentition, cardiovascular, gastrointestinal, musculoskeletal and neurological systems.

The physical examination is to be conducted by the Investigator or designated fully trained representative and assessed as normal, abnormal - not clinically significant or abnormal – clinically significant.

7.3.6 Body Height and Weight

Body height and weight will be recorded at V1 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.

At V2 and V6 only body weight will be recorded.

7.3.7 Vital Signs

Vital signs (systolic and diastolic blood pressure, respiratory rate and pulse rate) will be recorded at each visit from V1 to V6. At V2 (Day -1, Day 1 and Day 2) and V6 (Day 30) vital signs are to be checked prior to any product use and at the end of the day/at discharge.

All parameters will be recorded in supine position after subject has rested for at least 5 minutes. The subject should have abstained from smoking or using P3P for at least 15 minutes prior to measurement.

7.3.8 Electrocardiogram

A standard 12-lead ECG will be recorded after subject has rested for at least 10 minutes in supine position at each visit from V1 to V6. 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. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents.

7.3.9 Spirometry

Spirometry will be performed in accordance with the 2005 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry (36). Spirometry predicted values will be standardized to the European Community for Coal and Steel (ECCS) reference equations as published in the 1993 ERS statement (37).

Assessed parameters will include: FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEF 25, FEF 25 % predicted, FEF 75, FEF75 % predicted, FEF 25-75, FEF 25-75 % predicted, FEV_1/FVC. The ratio FEV1/FVC will be calculated from the highest acceptable FEV1 and the highest acceptable FVC respectively.

Spirometry without (pre-) and with (post-) bronchodilator will be performed at Screening (V1). The pre- and post-bronchodilator spirometry will be used for assessment of eligibility to the study. All post-bronchodilator spirometry testing will be performed 15-30 minutes post administration of around 400 µg of salbutamol/albuterol (usually equivalent to 4 puffs assuming 100 µg/puff). The time of salbutamol/albuterol inhalation and time of spirometry assessment will be recorded in the source document.

Spirometry without bronchodilator will be performed at V2: Day -1 before and after product test, Day 1 and Day 2 before product exposure and at the end of the daily product exposure; V3; V4; V5; V6: Day 29 at arrival on site and Day 30 prior to discharge.

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 after resting for at least 15 minutes and at least 1 hour after having stopped using cigarettes or P3P. Spirometry should be performed after assessment of vital signs and ECG.

7.3.10 Chest X-ray

During V1 a chest X-ray (anterior-posterior and left lateral views) will be assessed to exclude subjects with relevant pulmonary diseases. Subjects will be referred to a radiology facility for this procedure. No new examination is required if the subject can present at V1, a chest X-ray not older than 6 months with anterior-posterior and left lateral views. Available chest computed tomography (CT) or chest magnetic resonance imaging (MRI) results, or radiologist report from an equivalent radiological assessment, not older than 6 months can be accepted by Investigator for this purpose instead of chest X-ray. All reports have to be interpreted by a radiologist.

7.4 Biomarker Assessment

7.4.1 Biomarkers of Exposure to Nicotine

7.4.1.1 Nicotine in plasma

For PK analysis of plasma nicotine levels, venous blood samples will be obtained at Day 1 (V2) and Day 30 (V6) according to the investigational site standard operating procedures (SOPs). A total of 11 blood samples will be taken. Three samples will be taken prior to product use (T_0): 1 hour ± 5 minutes, 30 minutes ± 5 minutes and 5 minutes ± 2 minutes before T_0. Thereafter in relation to T_0, blood will be drawn at the following time points: after 4 minutes ± 1 minute, after 7 minutes ± 1 minute, after 10 minutes ± 1 minute, after 15 minutes ± 2

minutes, after 30 minutes ± 2 minutes, after 1 hour ± 5 minutes, after 2 hours ± 5 minutes and after 4 hours ± 5 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. Detailed procedures for handling of samples are described in the separate sample handling manual (SHM)/lab manual.

7.4.1.2 Nicotine Equivalents in Urine

Nicotine Equivalents (NEQ): molar sum of nicotine, cotinine, trans-3′-hydroxycotinine, nicotine-N-glucuronide, cotinine-N-glucuronide and trans-3′-hydroxycotinine-O-glucuronide will be measured in spot urine at Admission (Day -1; V2), and V3-V6. The results will be normalized to urine creatinine and expressed as concentration adjusted for creatinine.

7.4.2 Other Biomarkers of Exposure in Urine

At V2-V6, total NNAL and CEMA will be measured in spot urine. The results will be normalized to creatinine and expressed as concentration adjusted to creatinine.

7.4.3 Creatinine in urine

Creatinine will be measured in spot urine for normalization of urinary BoExp.

7.4.4 CYP2A6 Activity

CYP2A6 activity will be assessed on Day 1 (V2) and Day 30 (V6) 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.

7.5 Laboratory Assessments

7.5.1 Clinical Chemistry, Hematology, and Urine Analysis Safety Panel

A blood sample for hematology and clinical chemistry analysis will be taken from each subject at V1, V2, V4 and V6. Subjects should be fasting for at least 6 hours prior to sampling, except at V1 and early termination where non-fasting samples can be used. Tests will be conducted at a local laboratory (Appendix B). If during screening period a blood sample is not suitable for analysis (e.g. blood clotting) a re-test shoud be performed for the specific parameters which are not available. A urine sample will also be collected from each subject for urine analysis. Parameters to be tested are listed in Table 2.

Table 2 Clinical Laboratory Parameters for Safety Panel

Hematology	Clinical Chemistry	Urine Analysis

• Hematocrit
• Hemoglobin
• Mean corpuscular hemoglobin
• Mean corpuscular hemoglobin concentration
• Mean corpuscular volume
• Platelet count
• Red blood cell count
• White blood cell (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
	• C-reactive protein (CRP)
		• pH
		• Bilirubin
		• Glucose
		• Nitrite
		• Red blood cell traces
		• Protein
		• Specific gravity

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

7.5.2 Serology

A test for hepatitis B (HbsAg), hepatitis C (HCV antibody) virus and human immunodeficiency virus (anti-HIV1/2) will be performed at V1. In case of positive results, the subject will be referred to appropriate medical care.

7.5.3 Urine Drug Screen

A urine drug screen will be performed at the site at V1 and V2. The urine will be screened for amphetamine type substances, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates. In case of a positive urine drug test, a retest will not be allowed in order to evaluate eligibility. In case of an inconclusive test, a retest can be performed but this needs to be done immediately after the inconclusive test.

7.5.4 Urine Cotinine Screening

A urine dip-stick cotinine test will be performed at V1 and V2 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). In case of a negative cotinine test, a retest will not be allowed in order to evaluate eligibility. In case of an inconclusive test, a retest can be performed but this needs to be done immediately after the inconclusive test.

7.5.5 Alcohol Breath Test

An alcohol breath test will be performed using an alcometer device at V1 and V2. In case of a positive alcohol test, a retest will not be allowed in order to evaluate eligibility. In case of an inconclusive test, a retest can be performed but this needs to be done immediately after the inconclusive test.

7.5.6 Urine Pregnancy Test

A urine pregnancy test will be performed for all female subjects at V1, V2, V4 and V6. Subjects with a positive urine pregnancy test or unclear results (from two repetitions) at V1 or V2 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. Pregnancies detected after enrollment will lead to discontinuation from the study (section 5.2).

7.6 Sample Handling, Storage, and Shipment

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

Detailed procedures for handling of samples are described in the separate sample handling manual (SHM). Safety laboratory samples will be destroyed as per laboratory local regulations. All other samples (except biobanking 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.

7.6.1 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 238 mL of blood will be drawn for this study including samples for determination of nicotine concentrations (around 99 mL), CYP2A6 activity (8 mL), serology (5mL), safety (around 80 mL) and biobanking (about 46 mL). This calculation is based on an individual volume of each sample of 4.5 mL for nicotine PK (of which 4 mL is needed for nicotine dosing and 0.5 mL for cannula rincing of saline solution), 4 mL for CYP2A6 analysis, 5 mL for serology, 20 mL for safety laboratory assessments and 23 mL for biobanking (5 mL for transcriptomic and 6 mL for each of the following: proteomic, lipidomic and

metabolomics). 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 the SHM/ lab manual.

7.6.2 Spot Urine Samples

Spot urine samples will be used for the urine drug screen, urine cotinine screen, urine pregnancy test, safety urinalysis, BoExp (NEQ, Total NNAL and CEMA) and creatinine analysis and for biobanking samples.

Spot urine for BoExp will be collected from V2-V6. Baseline values of BoExp will be assessed at V2 (Day -1) when spot urine should be collected prior to product test. At V6 (Day 29) spot urine should be collected before the start of the wash-out period.

Spot urine for biobanking will be collected at V2 (Day 1) and V6 (Day 30.

For spot urine collected for BoExp and biobanking, the time of collection as well as the total volume collected should be recorded.

7.6.3 Biobanking

Samples of urine and whole blood/plasma will be collected at V2 and V6 for biobanking and subsequent transcriptomic, proteomic, lipidomic and metabolomic profiling as follows:

- Samples will be collected from spot urine for lipidomic profiling (2 tubes of 2 mL each per timepoint), for metabolomic profiling (4 tubes of 10 mL each per timepoint) and for proteomic profiling (4 tubes of 10 mL each per timepoint).
- Whole blood for transcriptomic (RNA) profiling (2 tubes of 2.5 mL each per time point), plasma for proteomic profiling (6 mL of whole blood at each time point to obtain and store 4 x 0.5 mL of plasma), plasma for lipidomic profiling (6 mL of whole blood at each time point to obtain and store 2 x 1 mL of plasma), and plasma for metabolomic profiling (6 mL of whole blood at each time point to obtain and store 4 x 0.5 mL of plasma) will also be collected.

All samples intended for biobanking will be kept frozen and will be shipped to a central storage facility or a bioanalytical laboratory according to the laboratory manual. Analysis of the biobanking samples will not be part of the research study report and will be reported separately. After the final RSR is signed, samples will be stored for a maximum of 10 years.

7.7 Questionnaires

The subject questionnaires will be completed by the subjects directly. All subject-reported outcome data as well as instructions will be provided in the subject's local language.

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).

7.7.1 ABOUT™-Dependence

Global dependence on tobacco and nicotine-containing products will be assessed via a subject self-reported outcome measure at V2, and at V6 using the ABOUT™-Dependence Questionnaire (32, 38). The questionnaire includes two multi-items scales (attitudinal and behavioral) complemented by one single item assessment on urgency to use (i.e., time to first product use in the day).

Subjects will be asked to assess the questionnaire on a 5 point scale ranging:

- from “not at all” to “extremely” for the attitudinal scale;
- from “never” to “all the time” for the behavioral scale;
- from “0 to 5 minutes” to “more than 3 hours” for the urgency to use.

7.7.2 ABOUT™-Product Experience

Product Experience will be assessed via a subject self-reported outcome measure at V2 and V6 within 60 minutes after the P3P product use for PK assessment, using the ABOUT™-Product Experience Questionnaire, also part of the ABOUT™ Toolbox (32, 39).

The questionnaire consists of three multi-item scales and two single-item scales, arising from an adaptation and rewording of the modified cigarette evaluation questionnaire (mCEQ) (40) to RRPs and the Product Evaluation Scale (41).

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).

Subjects will be asked to assess the 12 items of the questionnaire on a 7-point scale, ranging from “not at all” to “extremely”.

7.7.3 Sensory Questionnaire

A sensory questionnaire will be completed by each subject at V2 and V6 within 60 minutes after the P3P product use for PK assessment (adapted from (42)). The sensory questionnaire 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.

Subjects will be asked to assess the 8 items of the questionnaire on a 7-point scale, ranging from "not at all" to "extremely".

7.7.4 Product Acceptance Questionnaire

In the context of tobacco harm reduction, alternative sources of nicotine offered need to be acceptable to smokers as substitutes for cigarettes (43).

At V2 and V6, subjects will complete the product acceptance questionnaire. This questionnaire will be used to assess product characteristics of P3P relevant to determine subjects' acceptability of the product. Subjects will be asked to rate P3P in terms of sensory attributes, ease of use and occasions of use.

A baseline version of the product acceptance questionnaire consisting of 5 questions will be answered at V2, while a 6-questions version containing an additional question asking about occasions of P3P use will be answered at V6.

7.7.5 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) (44).

The VAS craving will be completed multiple times by the subject in relation to the P3P product used for PK assessment at V2 and V6. The first assessment will be done 10 minutes ± 2 minutes prior to T_0. Thereafter in relation to T_0, the assessment is to be performed at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour ± 10 minutes, 2 hours ± 10 minutes and 4 hours ± 10 minutes. VAS will be assessed immediately after the collection of the time-matching PK samples.

7.7.6 Cough Assessment

At V2-V6, 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 and three Likert scales).

The VAS will assess how bothersome cough is to the subject, on a 10 cm scale 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.

7.8 Other Study Procedures

7.8.1 Product Use Diary

Subjects will enter the number of P3P consumables used per day, the number of cigarettes used per day, or/and other tobacco and nicotine containing products used per day in a product use diary from Day 1 (V2) until the Discharge at V6 (including during the visits). At V2, before they start using it, subjects will be trained on how to log into the designated website and complete the product use diary by site staff. For subjects who decide to quit using all tobacco and nicotine containing products the product use will no longer be captured.

Site staff should train the subject on the correct use of the subject diary and perform regular checks to ensure that the subject completes the diary in the frequency and the way required.

7.8.2 Puffing/inhalation behavior question

At V2 (Day 1) and V6 (Day 30), during the use of P3P for PK assessment the site staff will be asked to observe the puffing/inhalation behaviour of the subjects and answer a question related to it. The staff will evaluate if the subject is using P3P by:

- puffing and holding the aerosol in the mouth for a short time and then inhaling (i.e. like a cigarette);
- puffing and immediately inhaling (without holding the aerosol in the mouth); or
- puffing and immediately exhaling, without inhalation;

At V2 (Day 2), V3, V4, V5, V6 (Day 29), the subjects will also answer the same question about their own puffing/inhalation behaviour.

The Sponsor will provide training to the site staff prior to the study initiation related to the correct evaluation of this assessment. Subjects will also be trained on the correct evaluation of their puffing/inhalation behavior

7.8.3 Weighing of P3P Products

At V2 and V6, P3P used for PK assessment should be weighed before product use and as early as possible (but within maximum 1 hour) after the end of product use. The balance precision needed for product weighing is at milligram (mg) level. 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 is defined as any health-related event which is adverse or unfavorable and which either starts after ICF signature or represents a worsening of a health–related condition that existed at the time of that signature. Careful medical judgment is required to establish whether a clinical finding (including an abnormal laboratory result) is a true AE or just a manifestation of a preexisting health–related condition. An AE may or may not have a causal relationship with the study procedures or with the use of investigational product.

8.1.2 Serious Adverse Events

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

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

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

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

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

Clinical conditions that existed before the start of the period of collection of AEs and still ongoing at V1 (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 still ongoing at V1

(concomitant disease) 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.

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

During a 14-day Safety Follow-Up Period new AEs/SAEs will be recorded and ongoing AEs/SAEs will be followed-up by the study site. In general, AEs will be followed-up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found and until the end of the study. At the end of the Safety Follow-Up all subjects will be contacted via phone in order to check the status of the ongoing AEs and also to collect any new AEs/SAEs experienced by the subjects. Subjects should be contacted 14-days after Day 30. In case they cannot be reached two additional attempts at the next 2 consecutive days will be made. If the subjects cannot be reached after the three attempts they will be declared

lost to follow-up. Phone calls should be recorded in the source documents. 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 3 Intensity of Adverse Events

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

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

The Investigator must assess the causal relationship between the exposure to the IP 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 (22).

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

Any non-serious AE that is ongoing at the time of Discharge or early termination will be followed-up by the Investigator during the Safety Follow-Up Period until it has been resolved,

stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). The follow-up of the ongoing non-serious AEs will be done via a phone call performed at the end of the Safety Follow-Up Period.

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 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 [redacted], 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 [redacted] for safety surveillance purposes.

All the SAE report forms must be sent as an attachment to an e-mail message to [redacted] and the Sponsor:

[redacted]	E-mail:	[redacted]
	Fax number:	+41 [redacted]
	Address:	[redacted] Switzerland
Sponsor:	E-mail:	[redacted]
	Phone:	+ 41 [redacted]
	Address:	Philip Morris Products S.A. R&D Innovation Cube 5, Quai Jeanrenaud 2000 Neuchâtel Switzerland

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

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

The Investigator or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the 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). Whenever that grading scheme is not available for the laboratory result of concern, the Investigator should assess the severity and the clinical significance of that result using his/her medical judgment.

Abnormal laboratory test results detected at the Screening Visit whose CTCAE grades are 2 or higher or still are CTCAE grade 1 and deemed clinically significant are usually concomitant disease or a manifestation of one and must be recorded accordingly.

However, in some instances, they may be assessed as AEs (and therefore must be handled according to the directions 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 4:

Table 4 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 clinically significant test results or clinical examination findings should 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 [redacted] and Sponsor 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 any pregnancy case that was reported during the study, as determined by local regulations.

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the early termination procedures (section 9.5), as soon as practical after discontinuation and will enter the 14-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 events, including 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 events should be actively collected during the study visits.

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

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 (V1) will be performed within 3 weeks prior to enrollment at V2. 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 5.

Table 5 Time Schedule – Screening Visit [V1]

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
Prior to any other procedure		Collection of signed informed consent	
During the visit		Information on risks of smoking, smoking cessation advice and product debrief	
		Tobacco and nicotine containing products use history and habits	
		Demographic data	
		Medical history/ concomitant disease	
		Prior (within 4 weeks prior to V1) and concomitant medication	
		Physical examination	
		Body height, weight and calculated BMI	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**V1**	
		Vital signs	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
		Chest X-ray	If not performed within 6 Months prior to V1.
		Spirometry (pre-bronchodilator and then post-bronchodilator)	Has to be done at least 1 hour after smoking. After resting in sitting position for at least 15 minutes prior to testing. To be done after vital signs and ECG. Post-bronchodilator spirometry to be performed 15-30 minutes post administration of salbutamol
	✓	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	
		Review of inclusion/exclusion criteria based on all relevant assessments	Includes readiness to comply with study procedures and willingness to use P3P during the study; no intention to quit smoking in the next 2 months.
		P3P demonstration	Without product use.
		AE/SAE recording	If the Screening Visit is performed on two separate days the AE/SAE questions will be asked again.

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

9.2 Admission Visit

Visit 2 will consist of 3 consecutive days (Day -1, Day 1 and Day 2) with on-site overnight period. Admission, enrollment, product test and randomization will take place at the first day of the visit (Day -1) while nicotine PK will be assessed on the second day of the visit (Day 1), after an overnight nicotine abstinence period of at least 10 hours. Following the PK assessments, subjects will remain on-site and will be allowed to use up to 15 P3P products daily on Day 1 and Day 2. The assessments performed at the first day of V2 (Day -1) are listed in Table 6; the assessments performed at the second day of V2 (Day 1) are listed in Table 7 and the assessments performed at the third day of V2 (Day 2) are listed in Table 8.

Table 6 Time Schedule – First day of V2 (Day -1)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day -1**	
Before enrollment		Concomitant medication	
		Collection of spot urine for: - Urine drug screen - Urine cotinine screen - Pregnancy test (all female subjects)	
		Alcohol breath test	
		Review of Inclusion criteria 4, 5 and 7 and exclusion criteria 11, 13, 14 and 19	
Before enrollment		Information on risks of smoking, smoking cessation advice and product debrief	
Enrollment		Enrollment	
After enrollment, before product test	✓	Clinical laboratory parameters (hematology, clinical chemistry)	After at least 6 hours of fasting.
		Collection of spot urine for: - Urinalysis safety panel - BoExp and creatinine	
		Physical examination	
		Vital signs	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.
	Body weight	
	Cough assessment	VAS and Likert
	Spirometry (without bronchodilator)	Has to be done at least 1 hour after smoking. After resting in sitting position for at least 15 minutes. To be done after vital signs and ECG.
Product test	Alternate use of P3P-1mg and P3P-2mg with up to 6 products in total	A wash-out period from any tobacco/nicotine containing products of at least 4 h prior to product test must be respected
After product test	Collection of used and unused products	
After product test and before randomization	Confirmation that subject is willing to use P3P during the study	
	Randomization	
	Vital signs	At least 5 min in supine position prior to measurement. At least 15 min after P3P use.
	Spirometry	To be done at least 1 hour after P3P use. After resting in sitting position for at least 15 minutes.
	Dinner	
Evening	Start of at least 10h nicotine wash-out period	
During the visit, after enrollment	Provide access and training for filling in questionnaires and product use diary	
During the visit, after enrollment	ABOUT™-Dependence questionnaire	
During the visit, after enrollment	Concomitant disease status check	Provide stop date if available
Ongoing	AE/SAE recording	
During product test	Product events malfunctions/misuse	

Abbreviations: ABOUT = Assessment of behavioral outcomes related to tobacco and nicotine products; AE = Adverse event; BoExp = Biomarkers of Exposure; ECG = Electrocardiogram; SAE = Serious adverse event; VAS = Visual analogue scale

Table 7 Time Schedule – Second day of V2 (Day 1)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
Prior to product use	✓	Blood sampling for CYP2A6 assessment	
Prior to breakfast/snack	✓	Blood sampling for biobanking	After at least 6 hours of fasting
		Collection of spot urine for biobanking	
At least 1h prior to start of product use		Light snack	e.g. biscuit, zwieback, fruit After biobanking blood sampling
Prior to product use		Vital signs	At least 5 min in supine position prior to measurement.
Prior to product use		Spirometry	After resting in sitting position for at least 15 minutes. To be done after vital signs.
Prior to product use (within 2 hours)		Weighing of product	
Prior to product use	✓	Blood sampling for baseline nicotine level	Prior to T_0 blood will be drawn at the following timepoints: 1 hour ± 5 min before T_0, 30 min ± 5 min before T_0, 5 min ± 2 min before T_0
10 ± 2 min prior to T_0		VAS-craving: baseline	
Just before T_0		Piercing of P3P capsule by site staff	
Start of product use = T_0		Product use	Single product for a duration of up to 15 minutes.
During/after product use	✓	Blood sampling for nicotine PK assessment	Post T_0, blood will be drawn at the following time points: 4 minutes ± 1 minute after T_0, 7 minutes ± 1 minute after T_0, 10 minutes ± 1 minute after T_0, 15 minutes ± 2 minutes after T_0, 30 minutes ± 2 minutes after T_0, 1 hour ± 5 minutes after T_0, 2 hours ± 5 minutes after T_0, 4 hours ± 5 minutes after T_0.

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
During/after product use		VAS-craving	Post T_0, 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)
During product use		Puffing/inhalation behavior question	Assessment performed by site staff.
Within 60 min after product use		Collection and weighing of used product	
Within 60 min after product use		Questionnaires: - ABOUT ™-product experience - Product acceptance - Sensory - Cough assessment	VAS and Likert
1 to 2 hours after T_0		Breakfast	
After the last blood collection for PK until 10:00 PM		On-site P3P use	Up to 14 P3P (15 in total including the one used for PK)
During the on-site product use period		Lunch and dinner	
After the end of daily product use		Vital signs	At least 5 min in supine position prior to measurement. At least 15 min after P3P use,
After the end of daily product use		ECG	After resting for at least 10 min in supine position.
1h after the end of daily product use		Spirometry	To be done at least 1 hour after P3P use. After resting in sitting position for at least 15 minutes. To be done after vital signs and ECG.
Ongoing		AE/SAE, concomitant medication recording	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 1**	
Ongoing		Product events malfunctions/misuse	

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

Table 8 Time Schedule – Third day of V2 (Day 2)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 2**	
Prior to product use		Vital signs	At least 5 min in supine position prior to measurement.
Prior to product use		Spirometry	After resting in sitting position for at least 15 minutes. To be done after vital signs.
6:30 AM - Discharge		On-site P3P use	Up to 15 P3P
During the visit		Puffing/inhalation behavior question	Answered by subjects.
Shortly before discharge		Vital signs	At least 5 min in supine position prior to measurement. At least 15 min after P3P use.
Shortly before discharge		Physical examination	
Shortly before discharge		ECG	After resting for at least 10 min in supine position.
Shortly before discharge		Spirometry	To be done at least 1 hour after P3P use. After resting in sitting position for at least 15 minutes. Done after vital signs and ECG.
At the end of the visit		Dispensing of P3P for ambulatory use	
After 6:30 PM		Discharge	
Ongoing		AE/SAE, concomitant medication recording	
Ongoing		Product events malfunctions/misuse	

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

9.3 Ambulatory Exposure Period

From check-out on V2 onwards, subject will use P3P up to 15 products daily in an ambulatory setting for 1 month. Subjects will come to the investigational site for weekly visits V3 (Day 7), V4 (Day 15), V5 (Day 22) and V6 (Day 29) with a visit time window of ± 2 days each. V6 will be a 2-day visit ie. subjects will remain on-site overnight and nicotine PK assessments will be performed on the second day of the visit, Day 30.

The study activities performed at V3-V5 are listed in Table 9.

Table 9 Time Schedule – V3, V4, V5

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
Beginning of the visit		Return of used and unused P3P consumables	
Beginning of the visit		Collection of spot urine for : - Pregnancy test (all female subjects) - Urinalysis safety panel - BoExp and creatinine	Pregnancy test and urinalysis safety panel only at V4.
During the visit		AE/SAE, concomitant medication recording	
During the visit		Product events malfunctions/misuse	
During the visit		Cough assessment	VAS and Likert.
During the visit		Puffing/inhalation behavior question	Answered by subjects.
During the visit	√	Clinical laboratory parameters (hematology, clinical chemistry)	Only at V4. After at least 6 hours of fasting.
During the visit		Vital signs	After resting for at least 5 min in supine position. At least 15 min after P3P use
During the visit		ECG	After resting for at least 10 min in supine position.
During the visit		Physical examination	
During the visit		Spirometry (without bronchodilator)	After resting in sitting position for at least 15 minutes. At least

Time	Blood Sample	Procedures	Additional Information
Start of Procedure			
			1h after P3P use. To be done after vital signs and ECG.
During the visit		Concomitant disease status check	Provide stop date if available
At the end of the visit		Dispensing of P3P	

Abbreviations: AE = Adverse event; BoExp = Biomarkers of Exposure; ECG = Electrocardiogram; SAE = Serious adverse event

The study activities performed on Day 29 (the first day of V6) are shown in Table 10.

Table 10 Time Schedule – First day of V6 (Day 29)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 29**	
Beginning of the visit		Return of used and unused P3P consumables	
Before start of nicotine wash-out		Collection of spot urine for: - Pregnancy test (all female subjects) - BoExp and creatinine	
		Vital signs	At least 5 min in supine position prior to measurement. At least 15 min after P3P use
		Spirometry	After resting in sitting position for at least 15 minutes. At least 1h after P3P use.To be done after vital signs.
		Cough assessment	VAS and Likert.
		Puffing/inhalation behavior question	Answered by subjects.
		Dinner	
Evening		Start of at least 10h nicotine wash-out period	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 29**	
During the visit		Information on risks of smoking, smoking cessation advice and product debrief	
During the visit		Concomitant disease status check	Provide stop date if available or indicate as ongoing
During the visit		AE/SAE, concomitant medication recording	
During the visit		Product events malfunctions/misuse	

Abbreviations: AE = Adverse event; BoExp = Biomarkers of Exposure; SAE = Serious adverse event; VAS = Visual analogue scale

The study activities performed on Day 30 (the second day of V6) are shown in Table 11.

Table 11 Time Schedule – Second day of V6 (Day 30)

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 30**	
Prior to product use	✓	Blood sampling for CYP2A6 assessment	
Prior to breakfast/snack	✓	Blood sampling for biobanking	After at least 6 hours of fasting.
Prior to breakfast/snack	✓	Clinical laboratory parameters (hematology, clinical chemistry) Collection of spot urine for: - Urinalysis safety panel - Biobanking	After at least 6 hours of fasting.
At least 1h prior to start of product use		Light snack	e.g. biscuit, zwieback, fruit After biobanking blood sampling
Prior to product use		Vital signs	At least 5 min in supine position prior to measurement.
Prior to product use (within 2 hours)		Weighing of product	
Prior to product use	✓	Blood sampling for baseline nicotine level	Prior to T_0 blood will be drawn at the following timepoints:

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 30**	
			1 hour ± 5 min before T_0, 30 min ± 5 min before T_0, 5 min ± 2 min before T_0.
10 ± 2 min prior to T_0		VAS-craving: baseline	
Just before T_0		Piercing of P3P capsule	
Start of product use = T_0		Product use	Single product for a duration of up to 15 minutes.
During/after product use	✓	Blood sampling for nicotine PK assessment	Post T_0, blood will be drawn at the following time points: 4 minutes ± 1 minute after T_0, 7 minutes ± 1 minute after T_0, 10 minutes ± 1 minute after T_0, 15 minutes ± 2 minutes after T_0, 30 minutes ± 2 minutes after T_0, 1 hour ± 5 minutes after T_0, 2 hours ± 5 minutes after T_0, 4 hours ± 5 minutes after T_0.
During/after product use		VAS-craving	Post T_0, 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)
During product use		Puffing/inhalation behavior question	Assessment performed by site staff.
Within 60 min after product use		Collection and weighing of used product	
Within 60 min after product use		Questionnaires: - ABOUT™-product experience - Product acceptance - Sensory - ABOUT™-dependence	
1 to 2 hours after T_0		Breakfast	

Time	Blood Sample	Procedures	Additional Information
Start of Procedure		**Day 30**	
Shortly before discharge		Vital signs	At least 5 min in supine position prior to measurement. At least 15 min after P3P use
		ECG	After resting for at least 10 min in supine position prior to recording.
		Physical examination	
		Body Weight	
		Spirometry	After resting in sitting position for at least 15 minutes. At least 1 h after P3P use. To be done after vital signs and ECG
During the visit		AE/SAE, concomitant medication recording	
During the visit		Product events malfunctions/misuse	

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

9.4 Safety Follow-Up Period

After Discharge on Day 30 or at the time of early discontinuation all enrolled subjects will enter a 14-day Safety Follow-Up Period during which new AE/ will be collected and ongoing AEs/SAEs will be followed-up by the site. The follow-up of ongoing AEs/SAEs will be conducted by the study investigational site as described in sections 8.2.2 and 8.2.6.

9.5 Early Termination Procedures

If 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
	Return of used and unused P3P consumables	
✓	Clinical laboratory parameters (hematology, clinical chemistry)	May be done in non-fasting state.
	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. At least 15 min after P3P use
	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. At least 1 h after P3P use. To be done after vital signs and ECG.
	Physical examination	
	Information on risks of smoking, smoking cessation advice	
	Concomitant disease status check	Provide stop date if available or note ongoing if ongoing at early termination
	AE/SAE, concomitant medication recording	
	Product events malfunctions/misuse	
	Discharge	

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

If a subject withdraws from the study or is discontinued during a planned visit, assessments required as per protocol for early termination that have been already performed during the planned visit should not be conducted again.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

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

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

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

During the study, the Monitor will have regular contact with the 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 and designees, 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

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

Further to the Investigator's meeting, 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.

The Monitor will also train the site staff on study procedures during the site initiation visit, and this training will be documented.

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. The electronic systems used to collect subject data, CRF and electronic patient reported outcome (ePRO), will be FDA 21 CFR Part 11 compliant.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

With the exception of the subject-reported outcome data, all results from the clinical assessments will be recorded in the source documents by the Investigator or their authorized designee(s) and then captured in the CRFs at the investigational site. The subject questionnaires and the daily product use (P3P, cigarettes, e-cigarettes or other) will be entered by the subject directly in a diary. 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. All subject reported outcome questionnaires including instructions will be provided in the subject's local language, and transcribed in the CRF in English. A CRF will be generated for all subjects who have signed 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, 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. 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 team at the CRO responsible for this study. The overall procedures for quality assurance of clinical study data are described in the SOPs of the CRO. The 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.

Data of all subjects that sign the ICF will be captured and stored in the study database. For Screen Failures the following information should be captured: date/time of ICF signature, date of birth, sex, race, AEs, concomitant medication given for treatment of 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 CRO.

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 generated electronically, and queries 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 the statistical analysis plan (SAP). The following statistical analyses will not be performed prior to the finalization of the SAP. Any changes to the planned statistical methods from the SAP will be documented in the research study report (RSR). The statistical evaluation will be performed using SAS®, version 9.2 or later.

12.1.1 Stratification Criteria

The sample randomization will enforce at least 40% of each sex in each product variant. Analyses stratified by sex will be detailed in the SAP.

12.1.2 Definitions for Statistical Data Analysis

For plasma nicotine time-concentration and VAS-craving, baseline will be defined as the last measurement prior to product use for PK assessment (prior to T_0)

For the changes from baseline in PK parameters, PD parameters, CYP2A6 and product acceptance, described in sections 3.1 and 3.2, Day 1 value will be considered as the baseline. For BoExp and safety parameters the last assessments prior to product test will be considered as baseline.

12.1.3 Descriptive Statistics

All data will be presented in listings.

All endpoints will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data, arithmetic means, 95% confidence intervals of the mean, and standard deviations (mean and SD), median, first and third quartiles, minimum and maximum. Change from baseline will be added to the summary statistics when applicable.

For log-normally distributed endpoints geometric mean, 95% confidence intervals of the geometric mean, geometric CV will be presented instead of arithmetic mean, 95% confidence intervals of the mean, and SD and percent change from baseline will be presented instead of change from baseline.

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.

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

In general, missing data will not be imputed.

For questionnaire data total scores and domain or subscale scores a certain degree of imputation may occur by averaging across individual item scores. Further details will be provided in the SAP.

For biological measurements, 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

A total of 60 subjects will be enrolled randomized with a 1:1 randomization ratio (~30 subjects randomized to P3P-1mg and ~30 to P3P-2mg). The sample size is empirically based.

12.3 Analysis Populations

Pharmacokinetic, pharmacodynamics, product acceptance, puffing/inhalation behavior endpoints will be analyzed using the PK population by actual product exposure and overall. Nicotine/tobacco containing product use, tobacco and nicotine containing product dependence, and CYP2A6 activity will be analyzed using the randomized population by actual product exposure and overall. Exposure to harmful and potentially harmful constituents will be analyzed using the randomized population. Safety will be analyzed using the safety population by actual product exposure and overall.
Actual product use exposure categories will be further defined in the SAP. Additional populations for sensitivity analysis could be defined in the SAP.

12.3.1 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.

12.3.2 Randomized population

The randomized population is a subset of the safety population and consists of all randomized subjects who had at least one post-randomization P3P use experience and have at least one valid non-safety assessment.

12.3.3 Pharmacokinetic Population

The PK population is a subset of the randomized population and consists of all subjects who completed at least one of the single use of P3P for PK assessment, and for whom at least one primary nicotine PK parameter can be derived. Only subjects without major protocol deviations, as defined in the SAP, which have an impact on evaluability of the primary objective will be included in the PK population.

Additional analysis sets may be defined in the SAP.

12.4 Demographics and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for the safety population, randomized population, and PK population.

Summaries will include sex, age, height, weight and BMI, smoking history, ABOUT Dependence Questionnaire, CYP2A6 activity and other endpoints that are only captured prior to product use.

These data will be summarized as described in section 12.1.3.

12.5 Primary Objective and Endpoints

12.5.1 Primary Endpoint Analysis Variables

PK endpoints are listed in section 3.1.

Nicotine PK parameters will be derived from plasma nicotine concentration versus time data. $AUC_{(0\text{-}4h)}$ will be derived using the trapezoidal method.

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 nicotine concentration data.

Baseline nicotine concentration (C_0) will be defined as the last measured concentration prior to T_0 of each visit. The baseline correction will be implemented by calculating the PK parameters using adjusted concentration values as described below (1):

- Calculate the slope using a linear regression on the log concentration of the 3 pre- T_0 timepoints.
- If the slope is <= 0, then use the slope to determine the elimination rate constant λ_z.
- If the slope is > 0, then use the average (geometric mean) of the subject's slopes that are <= 0 from the other visits to determine λ_z. If the subject's slopes are positive for all of the visits, baseline corrected PK parameters will not be calculated.
- Adjust each concentration value post-baseline using the following formula:

$$cC_t = C_t - C_0 * e^{-\lambda zt}.$$

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 nicotine concentration, λ_z is the elimination rate constant and t is the actual time.

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
ct_{max}	Time to maximum concentration cC_{max}
$cAUC_{(0-4h)}$	Background-corrected area under the plasma concentration-time curve from start of product use (T_0) to 4 hour

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

PK parameters will be summarized as described in section 12.1.3.

Nicotine PK profiles will be summarized and plotted over time for each visit.

An analysis of variance (ANOVA) will be conducted for Day 1 and Day 30 on background-corrected $AUC_{(0-4h)}$ and background-corrected C_{max} endpoints in the natural logarithmic scale. The model will include sex as a covariate. The results of this analysis for each of $cAUC_{(0-4h)}$ and cC_{max} will be presented as geometric least square means and 95% confidence intervals for each variant and least square mean ratio and 95% confidence intervals of P3P-2mg:P3P-1mg ratio.

For the ANOVA tests, the following hypothesis will be tested:
H_0: $\mu 1 = \mu 2$
H_1: $\mu 1 \neq \mu 2$
where $\mu 1$ and $\mu 2$ are the means (arithmetic or geometric) for each product variant, respectively.

12.6 Secondary Objectives and Endpoints

12.6.1 Secondary Endpoint Analysis Variables

12.6.1.1 PD endpoints

PD endpoints are listed in section 3.2.

VAS craving score and changes from baseline will be summarized by timepoint. In addition, AUC_{VAS} will be derived by P3P variant: $AUC_{VAS\ (0\text{-}4h)}$.

Sensory Questionnaire and ABOUT Product Experience Questionnaire will be described as detailed in section 12.1.3. Further details on the summary statistics of these questionnaires will be provided in the SAP.

12.6.1.2 Product Acceptance

Product acceptance questionnaire will be described as detailed in section 12.1.3. Further details on the summary statistics of this questionnaire will be provided in the SAP.

12.6.1.3 Product Use

Nicotine/tobacco containing product use will be derived from product use diary. Some further exploration based on BoExp levels could be added in the SAP. Product use and product use will be described as detailed in section 12.1.3.

12.6.1.4 Biomarkers of Exposure

Biomarkers of Exposure (NEQ, total NNAL, and CEMA) will be described as detailed in section 12.1.3.

12.6.1.5 CYP2A6

CYP2A6 will be described as detailed in section 12.1.3.

12.6.1.6 ABOUT Dependence

Product Dependence Questionnaire will be described as detailed in section 12.1.3. Further details on the summary statistics of this questionnaire will be provided in the SAP.

12.6.1.7 Product weighing

Amount of powder extracted from P3P during the PK assessment will be described as detailed in section 12.1.3. Further details will be provided in the SAP.

12.6.2 Statistical Analysis

An analysis of variance (ANOVA) will be conducted for Day 1 and Day 30 on VAS-craving endpoints in the linear scale following the same approach described in section 12.5.3 presenting LS Means and LS mean differences. Additional statistical analysis of secondary endpoints may be defined in the SAP.

12.6.3 Safety Endpoints

In general, all safety data will be listed and tabulated as described in section 12.1.3.

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; spirometry; ECG data; clinical chemistry, hematology, and urine analysis safety panel; physical examination; concomitant medications.

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.

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 product variant and change from baseline will be presented for laboratory parameters, ECG, respiratory symptoms, and vital signs. Shift tables will be provided for selected laboratory, spirometry, and ECG data.

12.6.4 Exploratory Analyses

There are no planned exploratory analyses.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

13.1.1 Investigator

Investigator:	Vasilyuk Vasily Bogdanovich, MD LLC Scientific Research Center Eco-Safety [redacted] Russia Phone: +7 [redacted] E-mail: [redacted]

13.1.2 Sponsor

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13.1.3 Other Responsibilities

CRO	[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, bioanalyses and storage for biobanking samples are shown in Appendix B.

13.2 Subject Confidentiality

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

The names 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.

13.3 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).

13.4 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans, X-rays and ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study and the actions taken will be maintained by the investigational site for the study, as required by ICH GCP (2) and any other applicable local or national regulations. For X-rays, at least the radiologist's assessment is required as source document. If the actual image is available, it can be stored on CD as well.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in section 8 of the ICH 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), subject diaries.
- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents (e.g., chest X-rays, ECGs, consultation reports, physical examination and laboratory records) or any electronically captured study source data.
- Clinical laboratory reports, laboratory normal ranges.
- Original medical/hospital records, if applicable (the medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or study site).

- Record of any body fluids or tissue samples collected and retained.
- 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 will maintain documentation relating to the study as long as the IP is on the market, and three years after its discontinuation or for 15 years after the RSR has been finalized, whichever is longer.

13.5 Research Study Report

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

The RSR will be written based on standards of the ICH Guideline for the "Structure and Content of Clinical Study Reports"(45). In certain circumstances, an abbreviated RSR may be acceptable. Submission of the RSR to the IEC will be complied with as requested by local requirements.

13.6 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.

13.7 Publication and Disclosure Policy

This document contains information that is confidential and proprietary to the Sponsor. This information is being provided solely for the purpose of evaluation and/or conducting this study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IEC, or duly authorized representatives of regulatory agencies for this purpose under the

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

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

13.8 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.

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15 APPENDICES

Appendix A – Schedule of Events

	Screening	Admission	Product use period (up to 15 products/day)						Discharge	Early termination	Safety Follow-Up
Visit	**1**	**2**			**3**	**4**	**5**	**6**			
Study day	**-22 to -2**	**-1**	**1**	**2**	**7 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**30 ±2d**		**+14 days**
Informed consent	●										
Information on the risks of smoking/ smoking cessation advice and debriefing on P3P	●	●						●		●	
Inclusion/exclusion criteria [a]	●	●									
Tobacco and nicotine containing products use history and habits	●										
P3P demonstration	●										
Demographics	●										
Medical history/concomitant diseases	●										
Chest X-ray [b]	●										
B: HIV, Hepatitis B and C	●										
U: Drug screen	●	●									
U: Cotinine test	●	●									
U: Pregnancy test	●	●				●		●		●	
Alcohol breath test	●	●									
Vital signs [c]	●	●	●	●	●	●	●	●	●	●	
Physical examination	●	●		●	●	●	●		●	●	
Body height, weight and BMI [d]	●	●							●		
Spirometry [e]	●	●	●	●	●	●	●	●	●	●	
Prior/concomitant medication	●	●	●	●	●	●	●	●	●	●	●[f]

	Screening	Admission	Product use period (up to 15 products/day)						Discharge	Early termination	Safety Follow-Up
Visit	**1**	**2**			**3**	**4**	**5**	**6**			
Study day	**-22 to -2**	**-1**	**1**	**2**	**7 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**30 ±2d**		**+14 days**
B/U: Hematology, clinical chemistry, urinalysis safety panel	●	●				●			●	●	
ECG	●	●	●	●	●	●	●		●	●	
Enrollment		●									
P3P product test [g]		●									
Willing to continue to use P3P for 1 Month (confirmation after product test)		●									
Randomization		●									
B: CYP2A6 activity [h]			●						●		
Overnight nicotine wash-out period [i]		●						●			
P3P single product use for PK assessment [j]			●						●		
Weighing of P3P [k]			●						●		
Collection of used and unused P3P [l]					●	●	●	●		●	
On-site product use (up to 15 P3P)			●	●							
P3P resupply				●	●	●	●				
B: nicotine in plasma [m]			●						●		
U: BoExp [n]		●			●	●	●	●			
B/U: Biobanking			●						●		
Product use diary [o]			●	●	●	●	●	●	●		
ABOUT™-Dependence Questionnaire		●							●		
ABOUT™-Product Experience			●						●		
Product acceptance			●						●		

	Screening	Admission	Product use period (up to 15 products/day)						Discharge	Early termination	Safety Follow-Up
Visit	**1**	**2**			**3**	**4**	**5**	**6**			
Study day	**-22 to -2**	**-1**	**1**	**2**	**7 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**30 ±2d**		**+14 days**
Sensory Questionnaire			●						●		
VAS Craving [p]			●						●		
Puffing/inhalation behavior question (assessed by site staff)			●						●		
Puffing/inhalation behavior question (assessed by subject)				●	●	●	●	●			
Cough assessment (VAS, Likert scale)		●	●		●	●	●	●			
AE/SAE reporting	●	●	●	●	●	●	●	●	●	●	● [q]
Concomitant disease status		●			●	●	●	●		●	
P3P product event reporting		●	●	●	●	●	●	●	●	●	

Abbreviations: ABOUT = Assessment of Behavioral Outcomes related to Tobacco and nicotine products; AE = Adverse event; B = Blood sample; BMI = Body mass index; BoExp = Biomarkers of Exposure; ECG = Electrocardiogram; PK = Pharmacokinetics; SAE = Serious adverse event; U = Urine sample; VAS = Visual analog scale

a. Prior to enrollment, at Day -1 the following eligibility criteria will be re-checked: Inclusion criteria: smoking status confirmed by urine cotinine, subject is not planning to quit smoking within 2 months, subject is available for the entire study period and is willing to comply with the study procedures. Exclusion criteria: urine pregnancy test (all females), urine drug screen and alcohol breath test. The following eligibility criteria will only be checked at Day -1: Exclusion criteria: subject has received medication which has an impact on CYP2A6 activity within 14 days or within 5 half-lives of the drug prior to Day -1 (whichever is longer)

b. Pre-study chest X-ray (with anterior-posterior and left lateral views). Available chest computed tomography (CT) or chest magnetic resonance imaging (MRI) results, or radiologist report from an equivalent radiological assessment within 6 months prior to Screening.

c. Systolic and diastolic blood pressure, pulse rate, and respiratory rate. At V2 (Day -1, Day 1 and Day 2) and V6 (Day 30) vital signs are to be checked prior to any product use and at the end of the day/at discharge.

d. Subjects with a BMI < 18.5 kg/m^2 or BMI ≥ 32 kg/m^2 will be excluded. At V2 and V6 weight only will be recorded.

e. Spirometry with and without bronchodilator performed at Screening. Spirometry without bronchodilator performed at the remaining visits. At Day -1, spirometry will be performed before and after product test. At Day 1 and Day 2 spirometry will be performed before product use and at the end of the daily product use.

f. Only medication used for treatment of an AE/SAEs

g. P3P product test using up to 6 P3P products (both P3P-1mg and P3P-2mg) will be conducted at Day -1 after enrollment. A wash-out period from any tobacco/nicotine containing products of at least 4 h prior to product test is needed.

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

i. Starting on the first day of each confinement period, subjects will abstain from tobacco/nicotine containing products for at least 10 h prior to P3P use for PK assessment on the second confinement day.

j. Use of a single product with puffing depending on the subjects preference (*ad libitum* use) for a duration of up to 15 minutes.

k. Each P3P used for PK assessment should be weighed prior to product use and within 1h after the end of the use.

l. On Day 29 collection of unused P3P should occur right before the start of the 10h wash-out period.

m. A total of 11 blood samples will be taken for PK parameter estimation at Day 1 and Day 30. Three blood samples will be taken prior to the start of product use (T_0) 1 hour ± 5 minutes, 30 minutes ± 5 minutes and 5 minutes ± 2 minutes before T_0. Thereafter in relation to T_0, blood will be drawn at the following time points: after 4 minutes ± 1 minute, after 7 minutes ± 1 minute, after 10 minutes ± 1 minute, after 15 minutes ± 2 minutes, after 30 minutes ± 2 minutes, after 1 hour ± 5 minutes, after 2 hours ± 5 minutes and after 4 hours ± 5 minutes.

n. NEQ, NNAL and CEMA will be analyzed in spot urine and adjusted for creatinine.

o. Daily during the exposure period. Use of P3P and any other tobacco and nicotine containing products will be captured in a diary starting from Check-out of Day 1 until Discharge at Day 30.

p. First assessment to be done 10 ± 2 minutes prior to T_0. Thereafter, in relation to T_0, assessment is to be performed at 4 minutes ± 2 minutes, 10 minutes ± 2 minutes, 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hour and 4 hours ± 10 minutes each.

q. At the end of Safety FU (end of V6 + 14 days) the site will call all subjects to collect new AEs/SAEs and to follow-up ongoing AEs/SAEs. If the subject is not responding at the initial call, 2 additional attempts on the next consecutive days will be made in order to reach the subject

Appendix B - Participating Laboratories

Bioanalytical laboratory (plasma nicotine and CYP2A6 analysis; urinary BoExp and creatinine):

[redacted]

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

[redacted]
Russia

[redacted]
Russia

Samples shipment:

[redacted]
Russia

Biobanking of samples:

[redacted]
Germany

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] (mg/dL)	>ULN - 300;	>300-400;	>400-500;	>500;

Serum Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
(mmol/L)	>ULN - 7.75	>7.75-10.34	>10.34-12.92	>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
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]				

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
(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.