STATISTICAL ANALYSIS PLAN

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

Study Product: P3P

Sponsor Reference No.: P3P-PK-01-CH
CRO Study Code: [redacted]

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs).

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3 INTRODUCTION

This SAP has been developed to supplement the statistical analyses described in the clinical study protocol final version 1.0 dated 24 July 2017.

This SAP describes the methodology and considerations of the planned analyses and a list of all the TFLs for this study. A detailed description of the planned TFLs will be provided in a separate TFL shells document. Any changes to the TFL shells numbering or to the title of the TFLs will not require an amendment to this SAP.

This SAP and any amendments will be finalized prior to the lock of the clinical database. Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses, will be described in the clinical study report (CSR).

The preparation of this SAP is based on the following documents:

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" (**ICH Guideline E9, 1998**).
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" (**ICH Guideline E3, 1995**).
- Case report forms (CRF) final version 1.0 dated 25 AUG 2017.
- Randomization Plan version 2.0 dated 16 OCT 2017.

3.1 Revision History

Version	Date of Revision	Revision
Draft version 0.1	22SEP2017	[redacted] issued the first draft
Draft version 0.2	30NOV2017	[redacted] implemented the changes agreed with [redacted] and [redacted]
Draft version 0.3	18JAN2017	[redacted] implemented the changes required by [redacted] and [redacted]
Draft version 0.4	02MAR2018	[redacted] implemented the changes required by [redacted] and [redacted]
Final version 1.0	09MAR2018	[redacted] implemented the changes required by [redacted] and [redacted] and issued the final version 1.0 after Sponsor's approval

Version	Date of Revision	Revision
Draft version 1.1	25APR2018	[redacted] [redacted] updated sections 7.1.2.3, 12.6.2.2.1, 13.1.3.1, 13.1.4 and 16.2 (Table 21) and the numbering of figures 15.1.4 as agreed with [redacted] and [redacted] The update occurred prior to database lock but after the review of the draft results of the PK interim analysis In section 7.1.2.3 it was clarified that the considerations regarding the period of estimation, the number of data points included into the calculation and the goodness of fit for apparent terminal elimination half-life can be applied only in case of non-compartmental analysis In section 12.6.2.2.1 were added the new individual VAS craving result-time profiles In section 13.1.3.1 it was clarified how to manage for the calculation of the PK parameters the background-corrected values that are below the bioanalytical LOQ threshold In section 13.1.4 it was clarified which are the model-based estimated PK parameters whose geometric mean and CV% have to be presented In section 16.2 (Table 21) and wherever applicable the numbering of figures was updated due to the insertion of the new individual VAS craving result-time profiles
Final version 2.0	30APR2018	[redacted] issued the final version 2.0 after Sponsor's approval

4 ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used within this SAP.

Adapted mCEQ	Adapted version of the modified cigarette evaluation questionnaire
AE/SAE	Adverse event/serious adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical therapeutic and chemical

$AUC_{ad\ lib\ (0-4h)}$	Area under the concentration-time curve from $T_{0\ ad\ lib}$ to 4h after $T_{0\ ad\ lib}$
$AUC_{fix\ (0-4h)}$	Area under the concentration-time curve from $T_{0\ fix}$ to 4h after $T_{0\ fix}$
BLOQ	Below the lower limit of quantitation
BMI	Body mass index
$C_{average}$	Average plasma nicotine concentration during *ad libitum* use period
CDTS	CRO deviation tracking system
CI	Confidence interval
C_{max}	Maximum plasma concentration
C_{peak}	Highest plasma nicotine concentration during *ad libitum* use period
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events and common toxicity criteria
CTMS	Clinical trial management system
C_{trough}	Trough plasma nicotine concentration during *ad libitum* use period
CV	Coefficient of variation
CYP2A6	Cytochrome P450 2A6
ECG	Electrocardiogram
EOS	End of study
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence
FVC	Forced vital capacity
GCP	Good clinical practice
HIV	Human immunodeficiency virus
HPT	Human puffing topography
ICF	Informed consent form
ICH	International conference on harmonisation
IP	Investigational product
LLOQ	Lower limit of quantitation

LS	Least squares
λ_z	Terminal elimination rate constant
MedDRA	Medical dictionary for regulatory activities
NCA	Non-compartmental analysis
PD	Pharmacodynamics
PK	Pharmacokinetic
PMI	Philip morris international
PT	Preferred term
QTcB	QT interval corrected using bazett's formula
QTcF	QT interval corrected using fridericia's formula
RRP	Reduced risk product
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SQ	Sensory questionnaire
$T_{0\ ad\ lib}$	Time point of start of first product use at the *ad libitum* use period
$T_{0\ fix}$	Time point of start of product use at the fixed puffing regimen
$t_{1/2z}$	Terminal elimination half-life
TFL	Tables, figures, and listings
t_{max}	Time to the maximum concentration
t_{peak}	Time to peak plasma nicotine concentration at the *ad libitum* use period
UBC	United biosource corporation
ULOQ	Upper limit of quantitation
VAS	Visual analogue scale
WHO	World health organisation

4.1 Definitions for Statistical Analysis

The following special terms are used in this SAP:

Baseline	For PK/PD analysis and VAS-craving assessment, baseline is defined as the last assessment prior to time point of start of product use at the fixed puffing regimen ($T_{0\ fix}$) for fixed puffing regimen and as the last assessment prior to time point of start of first product use at the *ad libitum* use period ($T_{0\ ad\ lib}$) for *ad libitum* use, for each study day of exposure. For all the other endpoints, the baseline is defined as the last available assessment prior to $T_{0\ fix}$ on Day 1, except for vital signs , where baseline is defined as the last assessment prior to $T_{0\ fix}$ for each study day of exposure.
Safety follow-up	After discharge on Day 5 or after discontinuation, a 7-day safety follow-up will be done
End of Study	The end of the study (EOS) for a subject is defined as either the Discharge at Day 5, or the date of early termination of the subject, plus the 7 days for the Safety Follow-up Period. The end of the whole study corresponds to the individual EOS of the last subject.
Enrollment	On Admission Visit for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily assessed and met.
Randomization	Assignment to the respective sequence of product use at Day 2.
Screen failure	Subject who signs the ICF but is not enrolled.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective and Endpoints

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

   Endpoints:

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

5.2 Secondary Objectives and Endpoints

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

   Endpoints:

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

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

   Endpoints:

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

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

   Endpoint:

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

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

   Endpoint:

   - Weight difference of P3P before and after use

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

   Endpoints:

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

5.3 Additional Endpoints

The following additional assessments will be made:

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

5.4 Study Hypotheses And Evaluation Criteria

5.4.1 Hypotheses

There is no statistical hypothesis to be tested.

5.4.2 Evaluation Criteria

Not applicable.

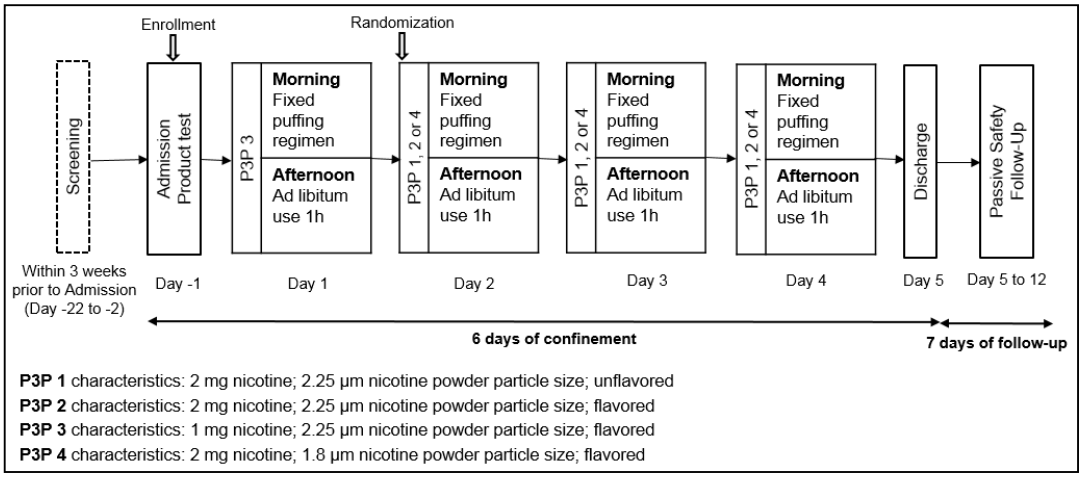
6 INVESTIGATIONAL PLAN

6.1 Study Design

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

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

Figure 1. Study Flowchart



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

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

The Admission Visit (Day -1)

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

The Confinement Period (Day -1 to Day 5)

On Day 1, after at least 10 hour abstinence from any tobacco/nicotine containing products, subjects will use P3P 3 during a fixed puffing regimen comprising of 12 puffs in total at a rate of one inhalation every 30 seconds (± 5 seconds) in the morning and during an *ad libitum* use period for 60 minutes (± 5 minutes) in the afternoon. The start of product use for fixed puffing and for the *ad libitum* use period will be defined as T0 fix and T0 ad lib, respectively. There will be a washout period of at least 10 hours between T0 fix and T0 ad lib.

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

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

PD effects related to craving will be assessed using a VAS scale at different timepoints. For the fixed puffing regimen the first assessment will be done 15 minutes ± 5 minutes prior to T0 fix, all other assessments will be done after T0 fix, at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. For the *ad libitum* use period the first assessment will

be done 15 minutes ± 5 minutes prior to T0 ad lib, all other assessments will be done after T0 ad lib, at 10 minutes ± 2 minutes, at 20 minutes ± 2 minutes, 30 minutes ± 5 minutes, 40 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. VAS will be assessed immediately after the collection of the time-matching PK samples.

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

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

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

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

Subjects discontinued after randomization will not be replaced.

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

On Days 2, 3 and 4, subjects will be instructed to use the assigned product variant for the given study day for a fixed puffing regimen in the morning and an *ad libitum* use period in the afternoon as described for Day 1. On each study day including Day 1, start of product use should be at approximately the same time for fixed puffing in the morning and for *ad libitum* use in the afternoon with at least a 10 hour washout period between T0 fix and T0 ad lib. There will be a washout period of at least 10 hours following T0 ad lib with respect to the T0 fix of the morning of the following study day to allow adequate background correction of the nicotine plasma concentrations. The assessments performed on Days 2, 3 and 4 will be the same as those described for Day 1.

On Day 5, there will be no product use, but subjects will remain at the investigational site for additional PK blood sampling for the purposes of estimating the terminal elimination half-life. A total of 5 blood samples will be taken in relation to T0 ad lib from the last product use at the following time points: T1 after 14 hours ± 30 minutes, T2 after 16 hours ± 30 minutes, T3 after 18 hours ± 30 minutes, T4 after 20 hours ± 30 minutes and T5 after 24 hours ± 30 minutes.

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

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

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

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

Any non-serious AE that is ongoing at the time of Discharge or early discontinuation will be followed-up by the Investigator or designee during the Safety Follow-Up Period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition) or lost to follow up.

At the end of the Safety Follow-Up Period, all ongoing non-serious AEs will be documented as "ongoing" and no further follow-up information will be sought for them by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly. All SAEs will be followed up by the Investigator or designee, despite their continuation, after the end of the Safety Follow-Up Period until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

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

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

6.1.1 Timing of Confinement Period

Subjects will return to the investigational site for Admission (Day -1) and will stay confined until Discharge on Day 5 or early termination.

6.2 Selection of Study Population

6.2.1 Inclusion Criteria

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

Inclusion Criteria	Rationale	Screening Visit	Admission Visit
1. Subject has signed the ICF and is able to understand the information provided in the ICF.	Administrative	X	
2. Smoking male or female aged between 21 and 65 years old.	Safety	X	
3. Subject is White.[a]	Effect	X	

Inclusion Criteria	Rationale	Screening Visit	Admission Visit
4. Subject has been a smoker for at least the last 3 years prior to the Screening Visit.	Effect	X	
5. Has smoked ≥ 10 commercially available cigarettes per day for 4 weeks prior to Screening Visit. Smoking status will be verified based on a urinary cotinine test (cotinine ≥ 200 ng/mL).	Effect	X	
6. Subject does not plan to quit smoking within 2 months after Screening Visit.	Safety	X	X
7. Smoking, healthy subject as judged by the Investigator or designee based on available assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG and medical history).	Safety	X	
8. Availability for the entire study period and willingness to comply with study procedures, including smoking interruptions.	Effect	X	X
9. Ready to accept using the P3P product.	Effect	X	

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

6.2.2 Exclusion Criteria

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

Exclusion Criteria	Rationale	Screening Visit	Admission Visit
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological and/or social reason).	Safety	X	

Exclusion Criteria	Rationale	Screening Visit	Admission Visit
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners, or subjects who are involuntarily incarcerated).	Administrative	X	
3. Subject has a clinically relevant disease which requires medication (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease) or any other clinically significant medical condition (including safety laboratory), which as per the judgment of the Investigator would jeopardize the safety of the subject.	Safety	X	
4. As per the Investigator's judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.	Effect	X	
5. Subject has donated or received whole blood or blood products within 3 months prior to Screening Visit.	Safety	X	
6. Subject has a BMI < 18.5 kg/m2 or > 32.0 kg/m2.	Safety	X	
7. Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer) which has an impact on CYP2A6 activity.	Effect		X

Exclusion Criteria	Rationale	Screening Visit	Admission Visit
8. Subject has a positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C.	Safety	X	
9. Subject has a positive alcohol breath test and/or a history of alcohol abuse that could interfere with the subject's participation in study.	Administrative	X	X
10. Subject has a positive urine drug test.	Administrative	X	X
11. Subject or one of their family members[b] is a current or former employee in the tobacco industry.	Administrative	X	
12. Subject or one of their family members[b] is an employee of the investigational site or of any other parties involved in the study.	Administrative	X	
13. Subject has participated in another clinical study within 3 months prior to the Screening Visit. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study.	Safety	X	
14. Subject has been previously screened or enrolled in this study.	Administrative	X	
15. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission Visit) or is breastfeeding.	Safety	X	X
16. For women of childbearing potential only[c]: subject does not agree to use an acceptable method of effective contraception.[d]	Safety	X	X
17. Use of estrogen-containing hormonal contraception or hormone replacement therapy	Effect	X	X

b. As defined by FDA guidance on Human Subject Protection (21 CFR 50.3(l), (m), 50.24(a)(6), (a)(7)(v), b)):

"Family member" means among other things "parent", "spouse", "brothers, sisters, and spouses of brothers and sisters" and "any individual related by affinity…whose close association with the subject is equivalent of a family relationship"

c. Women who are not of childbearing potential meet at least one of the following criteria:

Have undergone hysterectomy or bilateral tubal ligation,

Have medically confirmed ovarian failure, or

Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).

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

6.3 Product Allocation and Blinding

6.3.1 Methods of Assigning Subjects to Treatment Sequences

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

Table 1 Treatment Sequences

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

Details related to randomization procedures are provided in the randomization plan .

The enrolled subjects will be considered eligible for randomization if there are no safety concerns to continue in the study based on the Investigator's judgement.

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

Subjects discontinued after randomization will not be replaced.

At least 8 subjects of each sex will be randomized to ensure each sex represents at least 40% of the randomized population and thus no more than 10 subjects of the same sex will be randomized.

The treatment sequences will be assigned to the subjects through sequentially numbered opaque sealed envelopes (SNOSE method). The randomization letters will be generated through a dedicated SAS program as described in the randomization plan.

The randomization numbers will be assigned to the subjects eligible for randomization present at the clinical facility in the morning of Day 2 (they are confined since the evening of Day -1). The assignment should be performed according to the sequence of the subject numbers assigned during the screening visit.

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

The randomization scheme was generated by the CROSS' statistician who will be the only one having access to the live randomization codes prior to randomization together with the study monitor and the packaging provider, as detailed in the randomization plan. No one else of the study team, including study sponsor, CROSS and PI or the study subjects will be exposed to the live randomization codes prior to randomization.

6.3.2 Blinding

This study will be conducted as an open label study with no blinding. However, in order to prevent selection bias, Study Team (Sponsor and CROSS Alliance), Investigator, the subjects and the investigational site will be blinded to the randomization sequences until they are assigned as described in Section 6.3.1 "Methods of Assigning Subjects to Treatment Sequences".

6.3.3 Compliance to Product Allocation

Compliance will be ensured by strict distribution of the products (product by product) and collection of any used and unused investigational product by the designated site staff. The product accountability will be maintained by the investigational site staff and will include records for each product dispense and return.

7 DERIVED AND COMPUTED VARIABLES

Mean change from baseline is the mean of all individual subjects' change from baseline values (baseline is defined in Section 4.1 "Definitions for Statistical Analysis"). Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline.

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

$$\text{BMI}\left[\frac{\text{kg}}{\text{m}^2}\right] = \frac{10000 \times \text{Body Weight [kg]}}{(\text{Body Height [cm]})^2}$$

The QT interval corrected using Bazett's formula (QTcB) will be calculated as follows:

$$\text{QTcB interval [msec]} = \frac{\text{QT interval [msec]}}{\sqrt{\frac{60}{\text{Heart Rate [beats/min]}}}}$$

The QT interval corrected using Fridericia's formula (QTcF) will be calculated as follows:

$$\text{QTcF interval [msec]} = \frac{\text{QT interval [msec]}}{\sqrt[3]{\frac{60}{\text{Heart Rate [beats/min]}}}}$$

Note that the BMI, QTcB, QTcF are available in the data collected in the CRF and will not be recalculated.

The geometric coefficient of variation (CV) will be calculated using the following formula:

$$CV = 100\sqrt{e^{var} - 1}$$

where *var* is the variance from the log transformed data.

7.1 Pharmacokinetic Parameters

7.1.1 PK Analysis Materials

7.1.1.1 Analysis Dataset

The final PK analysis is to be performed on the quality controlled and quality assured data, as provided by the bioanalytical laboratory, after database lock.

7.1.2 PK Parameters

For PK parameters, baseline is defined in Section 4.1 "Definitions for Statistical Analysis".

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 concentration data for the fixed puffing regimen and *ad libitum* use. The baseline correction will be implemented by calculating the nicotine exposure parameters using adjusted concentration values. The plasma nicotine background-correction methodology will be confirmed following the conduct of an interim analysis as described in Section 13.1.3 "Interim Analysis Methods"

Nicotine PK parameters will be derived from both measured plasma nicotine concentrations, as well as the background-corrected plasma nicotine concentrations using noncompartmental analysis principles.

The actual blood sampling times post-exposure collected in the CRF will be used in the computation of the PK parameters, with the exception of pre-exposure sampling time which will be considered as time zero ($T_{0\ fix}$ or $T_{0\ ad\ lib}$).

PK parameters for the fixed regimen use will be derived using the nicotine concentration assessed between $T_{0\ fix}$ and the last available timepoint of the fixed regimen (4h±30min after product use). For the calculation of the AUC only, the window can be extended up to the pre-dose nicotine concentration before the *ad libitum* use.

PK parameters for the *ad libitum* use will be derived using the nicotine concentration assessed between $T_{0\ ad\ lib}$ and the last available timepoint of *ad libitum* use (4h±30 min after first product use). For the calculation of the AUC only, the window can be extended up to the pre-dose nicotine concentration before the next fixed regimen use or, in the last period only, to the additional samples collected.

The following PK parameters will be calculated, as per protocol background-corrected PK endpoints, for the fixed (Table 2) and *ad libitum* (Table 3) regimens.

Table 2 Background-corrected Fixed Regimen Nicotine Plasma PK Parameters

Parameter	Definition
cC_{max}	Background-corrected maximum observed plasma concentration.

Table 2 Background-corrected Fixed Regimen Nicotine Plasma PK Parameters

Parameter	Definition
ct_{max}	Time of background-corrected maximum observed plasma concentration.
$cAUC_{fix(0-4h)}$	Background-corrected area under the concentration-time curve from start of product use ($T_{0\ fix}$) to 4 hours

Table 3 Background-corrected Ad Libitum Regimen Nicotine Plasma PK Parameters

Parameter	Definition
cC_{peak}	Background-corrected peak plasma nicotine concentration
ct_{peak}	Time to peak plasma nicotine background-corrected concentration during *ad libitum* use, ct_{peak} will be reported as long as there is at least one quantifiable concentration post-exposure
$cAUC_{ad\ lib(0-4h)}$	Area under the concentration-time curve from start of product use ($T_{0\ ad\ lib}$) to 4 hours
cC_{trough}	Background-corrected trough plasma nicotine concentration from $T_{0\ ad\ lib}$ to 1 hour
$cC_{average}$ [a]	Background-corrected average of plasma nicotine concentration from $T_{0\ ad\ lib}$ to 1 hour

a $cC_{average}$ is calculated by estimating the area under the concentration-time curve using background-corrected nicotine concentrations from the start of product use up to the last available concentration within 1 hour post product use, divided by the collection interval

Uncorrected PK parameters will also be presented, and the corresponding estimated PK parameters are described in Table 4, for the fixed regimens, and in Table 5, for the *ad libitum* regimens.

Table 4 Fixed Regimen Nicotine Plasma PK Parameters (Uncorrected)

Parameter	Definition
C_{max}	Maximum observed plasma concentration.
t_{max}	Time of maximum observed plasma concentration.
$AUC_{fix(0-4h)}$	Area under the concentration-time curve from start of product use ($T_{0\ fix}$) to 4 hours

Table 5 Ad Libitum Regimen Nicotine Plasma PK Parameters (Uncorrected)

Parameter	Definition

Table 5 Ad Libitum Regimen Nicotine Plasma PK Parameters (Uncorrected)

Parameter	Definition
C_{peak}	Peak plasma nicotine concentration
$AUC_{ad\ lib(0-4h)}$	Area under the concentration-time curve from start of product use ($T_{0\ ad\ lib}$) to 4 hours
t_{peak}	Time to peak plasma nicotine concentration during *ad libitum* use, t_{peak} will be reported as long as there is at least one quantifiable concentration post-exposure
C_{trough}	Trough plasma nicotine concentration after from $T_{0\ adlib}$ to 1 hour
$C_{average}$ [a]	Average of plasma nicotine concentration from $T_{0\ ad\ lib}$ to 1 hour

a $C_{average}$ is calculated by estimating the area under the concentration-time curve from the start of product use up to the last available concentration within 1 hour post product use, divided by the collection interval

In addition, λ_z-related nicotine plasma PK parameters will be calculated following the last product use (Days 4 to 5), as shown in Table 6:

Table 6 Nicotine λ_z-related Parameters Following Last P3P Product Use (Days 4 to 5)

Parameter	Definition
Adjusted-R^2	Adjusted coefficient of determination for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z.
No. points λ_z	Number of points used in computing λ_z. If λ_z cannot be estimated, zero.
λ_z upper	Upper timepoint included in the calculation of λ_z.
λ_z lower	Lower timepoint included in the calculation of λ_z.
λ_z	Terminal elimination rate constant, estimated by linear regression analysis of the natural log-transformed concentration-time data
$t_{1/2z}$	Terminal elimination half-life

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

7.1.2.1 Calculation of C_{max}, t_{max}, C_{peak}, t_{peak} with and without baseline adjustment

The minimum requirement for the determination of the C_{max} is the inclusion of at least one quantifiable concentration within 1 hour post-exposure. C_{max}, t_{max}, C_{peak}, t_{peak} will be obtained directly from the plasma concentration-time profiles. If C_{max} (respectively C_{peak}) occurs at more than one time point, t_{max} (respectively t_{peak}) will be assigned to the first occurrence of the C_{max} (respectively C_{peak}).

The same approach will be applied for the corresponding baseline corrected PK parameters by using the nicotine concentration adjusted for baseline.

7.1.2.2 Calculation of AUC

The minimum requirement for the calculation of the *ad libitum* or fixed $AUC_{(0\text{-}4h)}$ is the inclusion of at least 3 plasma concentrations above the lower limit of quantitation (LLOQ), with at least 1 of these concentrations following C_{max}. For the ad libitum use, cases where C_{max} is achieved at 4 hours will be evaluated on individual basis.

The AUC will be set to missing if the last available concentration before 4 hours is not on the terminal phase of the individual time-concentration curve (as assessed by the goodnes of fit criteria defined in section 7.1.2.3) otherwise the first available concentration after 4 hours and before the next product use will be used for interpolating the concentration value at 4 hours for the fixed regimen use.

A similar approach will be used for the *ad libitum* use with the exception of the last period (day 4), where the first available concentration after 4 hours will be used for interpolating the concentration value at 4 hours.

The corresponding total exposure parameters or AUCs (e.g. $cAUC_{fix(0\text{-}4h)}$, $cAUC_{ad\ lib(0\text{-}4h)}$, etc.) will be calculated following the conventional linear trapezoidal method.

The same approach will be applied for the corresponding baseline corrected PK parameters by using the nicotine concentration adjusted for baseline.

7.1.2.3 Criteria for Calculating the Apparent Terminal Elimination Half-Life

If the calculation of the apparent terminal elimination half-life is performed according to the non-compartmental analysis (NCA), then it will be based on PK nicotine concentration samples from days 4 and 5 and on the following rules.

$t_{1/2}$ will be calculated according to the following formula:

$$t_{1/2} = \frac{\ln(2)}{\lambda_z}$$

where λ_z will be calculated by least squares (LS) linear regression of the terminal portion of the log-transformed plasma concentration-time curve.

The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. The concentrations included in the terminal elimination phase will be flagged in the data listings.

Period of Estimation

- Apparent terminal (elimination) half-lives will be calculated, where possible, over at least 3 half-lives. Where an apparent terminal half-life is estimated over less than 3 half-lives, it will be flagged in the data listings.

- An apparent terminal half-life will not be reported if it can only be calculated over a period that is less than 1.5 half-lives.

Number of Data Points

- At least 3 data points in the terminal phase with nicotine concentration greater than the LLOQ will be used for each subject in the regression analysis. An apparent terminal half-life will not be reported if derived from less than 3 data points. All available data points that are consistent with the assessment of a straight line on the log-transformed scale will be considered and always including the last quantifiable concentration but excluding the concentration at t_{max}.

Goodness of Fit

- When assessing apparent terminal phases, the coefficient of determination, R^2 adjusted value, will be used as a measure of the goodness of fit of the data points to the determined line. This parameter will be used as it is considered to be a better assessment of the goodness of fit, compared to R^2, as it adjusts for the number of points included in the line therefore allowing for a more direct comparison between elimination phases determined using different numbers of data points.
- Apparent terminal half-life will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.700.

If the calculation of apparent terminal elimination half-life is performed according to the compartmental analysis (CA), then it will be based on PK nicotine concentration samples from days 1 to 5 and all the considerations regarding the period of estimation, the number of data points included into the calculation and the goodness of fit will be no more applicable.

7.1.3 Anomalous Values

During the pre-analysis data review, nicotine concentration values will be reviewed for their inclusion in the analysis. If a concentration value is considered to be anomalous due to being inconsistent with the expected PK profile it will be flagged in the listings and if applicable in the figures.

Exclusion of abnormal concentrations (i.e. sudden increases or drops in concentration, inconsistent with a typical plasma nicotine PK profile) will be avoided, hence outlier values may only be excluded in the event there exists an explanation that clearly justifies such exclusion (e.g. protocol violation, documented sample handling errors, interuption of product use during fixed regimen, and/or analytical errors, best scientific judgment).

The reason for the exclusion of abnormal concentrations (if any) will be documented. If the exclusion has a meaningful impact on the overall interpretation of the results, then it will also be discussed between Certara and PMI and fully documented.

7.2 Biomarkers

7.2.1 CYP2A6

CYP2A6 activity is calculated in plasma as the metabolic ratio of trans-3' hydroxycotinine and cotinine, both expressed in molar equivalent (nmol/L) (**Jacob et al, 2011**):

$$\text{CYP2A6} = \frac{\text{HCOT[ng/mL]} \times 5.202}{\text{COT[ng/mL]} \times 5.675}$$

The conversion factor will be applied as follows:

Cotinine (COT)	The molecular weight is 176.2178 g/mol (**Chemical Information Specialized Information Services RN:486-56-6**) Therefore to transform COT from ng/mL to nmol/L, the result in ng/mL will be multiplied by 5.675
Trans-3'hydroxycotine (HCOT)	The molecular weight is 192.217 g/mol (**Chemical Information Specialized Information Services RN:34834-67-8**) Therefore to transform HCOT from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.202

The ratio will be reported as a percentage.

7.3 Questionnaires

7.3.1 VAS Craving Assessments

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).

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

For the *ad libitum* use period the first assessment will be done 15 minutes ± 5 minutes prior to $T_{0\ ad\ lib}$, all other assessments will be done after T0 ad lib, at 10 minutes ± 2 minutes, at 20 minutes ± 2 minutes, 30 minutes ± 5 minutes, 40 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each.

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

The actual VAS assessments times post-exposure collected in the CRF will be used in the computation of the AUC_{VAS}, with the exception of pre-exposure assessment time which will be considered as time zero ($T_{0\ fix}$ or $T_{0\ ad\ lib}$).

7.3.2 Fagerström Test for Nicotine Dependence

The FTND questionnaire will be used in its revised version (**Heatherton et al, 1991**) as updated in 2012 (**Fagerström et al, 2012**). The FTND questionnaire consists of 6 items as presented in Table 7. These questions are to be answered by the subject themselves. It is conducted at Screening only, to determine subject's dependence on nicotine.

Table 7 Scoring for the Fagerstrom Test for Nicotine Dependence

	FTND Question	Response	Score
1	How soon after you wake up do you smoke your first cigarette?	▪ After 60 minutes	0
		▪ 31-60 minutes	1
		▪ 6-30 minutes	2
		▪ Within 5 minutes	3
2	Do you find it difficult to refrain from smoking in places where it is forbidden?	▪ No	0
		▪ Yes	1
3	Which cigarette would you hate most to give up?	▪ The first one in the morning	1
		▪ Any other	0
4	How many cigarettes per day do you typically smoke?	▪ 10 or less	0
		▪ 11-20	1
		▪ 21-30	2
		▪ 31 or more	3
5	Do you smoke more frequently during the first hours after waking than during the rest of the day?	▪ No	0
		▪ Yes	1
6	Do you smoke if you are so ill that you are in bed most of the day?	▪ No	0
		▪ Yes	1

The FTND total score will be derived by summing the individual item scores if all items are non-missing, otherwise the total score will be set to missing.

For the FTND total score, descriptive statistics and frequency tables according to the following classification will be provided (**Fagerström et al, 2012**):

FTND total score	Classification value
0 - 3	Mild
4 - 6	Moderate
7 - 10	Severe

7.3.3 Adapted Modified Cigarette Evaluation Questionnaire

The adapted mCEQ will be completed by the subject him/herself daily (within 60 minutes after the end of the *ad libitum* use period) from Day 1 to Day 4 to assess 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)

The questionnaire to be used adapts the wording of mCEQ items (**Cappelleri et al, 2007**) to RRPs, following a similar approach with the Product Evaluation Scale (**Hatsukami et al. 2013**) which is an adaptation of the mCEQ for oral tobacco products.

The adapted mCEQ consists of 12 items as presented in Table 8. Items are assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity on that scale.

Table 8 Adapted mCEQ - Questions and Subscales

	Question	Subscale
1	Was it satisfying?	Product Satisfaction
2	Did it taste good?	Product Satisfaction
3	Did you enjoy the sensation in your throat and chest?	Enjoyment of Respiratory Tract Sensations
4	Did it calm you down?	Psychological Reward
5	Did it make you feel more awake?	Psychological Reward
6	Did it make you feel less irritable?	Psychological Reward
7	Did it help you concentrate?	Psychological Reward
8	Did it reduce your hunger for food?	Psychological Reward
9	Did it make you dizzy?	Aversion
10	Did it make you nauseated?	Aversion
11	Did it immediately relieve your craving for a cigarette?	Craving Reduction
12	Did you enjoy it?	Product Satisfaction

The subscales scores will be derived by averaging the relevant individual non-missing item scores if at least 50% are non-missing, otherwise the subscale score will be set to missing.

7.3.4 Sensory Questionnaire

The sensory questionnaire (Rose et al. 2010) will be completed by the subject him/herself daily (within 60 minutes after the end of the *ad libitum* use period) from Day 1 to Day 4 after each product use to assess 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.

The sensory questionnaire consists of 8 items as presented in Table 9. Items are assessed on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). Higher scores indicate greater intensity on that scale.

Table 9 Sensory Questionnaire - Questions

	Question
1	How much did you like the puffs you took?
2	How harsh were the puffs you took?
3	How similar to your own brand were the puffs?
4	Strength of puffs on tongue?
5	Strength of puffs in nose?
6	Strength of puffs in back of mouth & throat?
7	Strength of puffs in windpipe?
8	Strength of puffs in chest?

Each item will be analyzed individually (no subscales).

7.3.5 Cough Assessment

Subjects will be asked if they have experienced a regular need to cough (e.g., coughing several times) in the last 24 hours prior to assessment. If the answer is 'yes', they will be asked to complete a visual analogue scale (VAS), three Likert scale questions and an open question assessing their cough during previous 24 hours.

The VAS will assess how bothersome cough is to the subject ranging from 'not bothering me at all' to 'extremely bothersome', and this will be given a numeric value between 0 and 100.

Subjects will also be asked to assess the intensity and frequency of cough and the amount of sputum production on Likert scales as presented in Table 10.

Table 10 Cough Assessment Likert Scales

	Question	Likert Scale
1	How intense is your cough?	1 = very mild
		2 = mild
		3 = moderate
		4 = severe
		5 = very severe
2	How frequently do you normally have to cough each day?	1 = rarely
		2 = sometimes
		3 = fairly often
		4 = often
		5 = almost always
3	To what extent do you produce sputum when coughing?	0 = no sputum
		1 = a moderate amount of sputum
		2 = a larger amount of sputum
		3 = a very large amount of sputum

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

7.4 Human Puffing Topography

The following Human Puffing Topography Parameters will be measured per-puff:

Table 11 Human Puffing Topography Parameters Per-Puff

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

The following Human Puffing Topography Parameters will be calculated per-product use experience:

Table 12 Human Puffing Topography Parameters Per-Product Use

Description	Variable	Formula	Unit
Total number of puffs	NPC	Σ Ni	
Total puff volume	TVOL	Σ Vi	mL
Average puff volume	AvgVi	Σ Vi / NPC, i=1 ... NPC	mL
Average puff duration	AvgDi	Σ Di / NPC, i=1 ... NPC	sec
Total puff duration	TDi	Σ Di	sec
Average use flow	AvgQmi	Σ Qmi / NPC, i=1 … NPC	mL/sec
Average peak flow	AvgQci	Σ Qci / NPC, i=1 … NPC	mL/sec
Total inter puff interval	TIi	Σ Ii	sec
Average inter puff interval	AvgIi	Σ Qci / NPC, i=1 … NPC	sec
Total puffing duration	TDFi	Σ DFi	sec
Puffing Intensity	SMINT	TVOL/TDFi	mL/sec
Puffing Time Index	PTI	100*TDi)/TDFi	%
Puff Frequency	PFeq	NPC/(TDFi/60)	

7.5 Categorical Variables

Table 13 Categorical Variable Definitions

Variable	Categories	
BMI (kg/m^2)	Underweight:	< 18.5
	Normal range:	≥ 18.5 and < 25.0
	Overweight:	≥ 25.0 and < 30.0
	Obese:	≥ 30.0
FTND total score	Mild:	0 - 3
	Moderate:	4 - 6
	Severe:	7 - 10
Adverse event relationship to investigational product	Related	
	Not related	
Adverse event relationship to study procedure	Related	
	Not related	
Adverse event expectedness	Not Expected	
	Expected	

Table 13 Categorical Variable Definitions

Variable	Categories
Action taken with investigational product due to adverse event	None Product Use Reduced Product Use Interrupted Product Use Stopped Not Applicable Unknown
Severity of adverse event	Mild Moderate Severe
Outcome of adverse event	Recovered/Resolved Recovered/Resolved With Sequelae Recovering/Resolving Not Recovered/Not Resolved Fatal Unknown
Seriousness criteria of adverse event	Fatal Life-threatening Requires hospitalization Results in disability/incapacity Congenital anomaly/birth defect Other medically important event
Action taken with investigational product due to product event	Product Replaced Product Withdrawn Other
Severity of product event	Minor Major

8 SAMPLE SIZE JUSTIFICATION

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

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

we are expecting a low drop-out rate, 3 subjects will be allocated to each sequence. Therefore, 18 subjects will be randomized.

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

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

A sensitivity analysis was added in Section 12.6.1 "Primary Analyses" to evaluate the impact of incuding the Study Day in the analysis of specific PK parameters.

The definitions of enrolled population and randomized population were added.

No shift table for ECG data will be provided.

10 ANALYSIS POPULATIONS

All endpoints (other than safety) will be analyzed using the PK population. Safety will be analyzed using the safety population.

10.1 Screened Population

The screened population consists of all the subjects who signed ICF.

10.2 Enrolled Population

The enrolled population is a subset of the screened population consisting of all the subjects with enrollment or randomization date, or have at least one exposure to P3P (including the product test at Admission).

10.3 Randomized Population

The randomized population is a subset of the enrolled population consisting of all the subjects with a randomization date.

10.4 PK Population

The PK population consists of all the subjects in Screened Population who completed at least one single use of P3P (during Day 1 to Day 4) and for whom at least one primary nicotine PK parameter can be derived. Subject with major protocol deviations that impact evaluability of the data will be excluded the PK populations (see Section 11.1 "Major Protocol Deviations").

10.5 Safety Population

The safety population consists of all subjects in Screened Population who have at least one exposure to P3P (including the product test at Admission) and have at least one safety assessment post exposure.

11 PROTOCOL DEVIATIONS

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

Information following site monitoring and other reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and subsequently recorded in the CRO Deviation Tracking System (CDTS). Additional protocol deviations may be identified in the data review, these will also be recorded in the CDTS. All protocol deviations will be imported into the DV domain of the Study Data Tabulation Model (SDTM).datasets/Analysis Data Model (ADaM).

All deviations will be reviewed to determine their impact when subjects are assigned to analysis populations. Each deviation will be classified as major or minor; all major deviations will be further reviewed to determine whether or not the deviation impacts the evaluability of the results and therefore should result in the subject being excluded from the PK population.

11.1 Major Protocol Deviations

The following categories for the major deviations will include, but are not limited to the deviations presented in Table 14.

Table 14 Definition of Major Protocol Deviations

Category	Description
Entry Violation	Violation of inclusion/exclusion criteria
Mis-randomization	Violation of the product allocation process, including but not limited to the misclassification of subject's sex at randomization and incorrect P3P variant administered according to randomized sequence
Mis-use of product	• Use of any nicotine or tobacco–containing product other than P3P 3 at Day 1 or allocated P3P variants from Day 2 to Day 4 during the exposure periods, or use of any nicotine tobacco-containing product during wash-out hours.

Table 14 Definition of Major Protocol Deviations

Category	Description
	• Product use not compliant with planned regimen (e.g., number of puffs during the fixed regimen)
Concomitant medication	Use of any drugs which are known to affect CYP2A6 activity

Among the above criteria, violations of inclusion criteria 1, 2, 4, 5 and 7, or of the exclusion criteria 2 and 15 will be considered as impacting the evaluability. Other major protocol deviations will be assessed for their impact on the PK Population and evaluated during the pre-analysis data review meeting (Section 6.3.2 "Methods of Assigning Subjects to Treatment Sequences").

11.2 Minor Protocol Deviations

The categories for the minor deviations will include, but are not limited to the deviations presented in Table 15.

Table 15 Definition of Minor Protocol Deviation Categories

Category	Description
Procedural violation	Violation of any study procedures not affecting safety or data evaluability
Time deviation (Plasma nicotine PK sample)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Table 16)
Time deviation (other assessment)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Table 16)
Assessment missing (Plasma nicotine PK sample)	Assessment is missing
Assessment missing (other assessment)	Assessment is missing
Randomization sequence	Subject randomized not according to the sequence of the subject numbers assigned during the screening visit

11.3 Assessment Windows

Definition of Assessment Windows is described in Table 16:

Table 16 Definition of Assessment Windows

Assessment	Nominal Time point(s) (relative to $T_{0\ fix}$ or $T_{0\ ad\ lib}$)	Window
Plasma nicotine PK sample	15 minutes prior to $T_{0\ fix}$	± 5 minutes
	2 minutes after $T_{0\ fix}$	± 1 minute
	4 minutes after $T_{0\ fix}$	± 1 minute
	7 minutes after $T_{0\ fix}$	± 1 minute
	10 minutes after $T_{0\ fix}$	± 1 minute
	15 minutes after $T_{0\ fix}$	± 2 minutes
	30 minutes after $T_{0\ fix}$	± 2 minutes
	1 hour after $T_{0\ fix}$	± 5 minutes
	2 hours after $T_{0\ fix}$	± 5 minutes
	4 hours after $T_{0\ fix}$	± 5 minutes
	15 minutes prior to $T_{0\ ad\ lib}$	± 5 minutes
	10 minutes after $T_{0\ ad\ lib}$	± 1 minute
	20 minutes after $T_{0\ ad\ lib}$	± 2 minutes
	30 minutes after $T_{0\ ad\ lib}$	± 2 minutes
	40 minutes after $T_{0\ ad\ lib}$	± 5 minutes
	1 hour after $T_{0\ ad\ lib}$	± 5 minutes
	2 hours after $T_{0\ ad\ lib}$	± 5 minutes
	4 hours after $T_{0\ ad\ lib}$	± 5 minutes
	14 hours after $T_{0\ ad\ lib}$ (*)	± 30 minutes
	16 hours after $T_{0\ ad\ lib}$ (*)	± 30 minutes
	18 hours after $T_{0\ ad\ lib}$ (*)	± 30 minutes
	20 hours after $T_{0\ ad\ lib}$ (*)	± 30 minutes
	24 hours after $T_{0\ ad\ lib}$ (*)	± 30 minutes
Visual Analog Scale - Craving	15 minutes prior to $T_{0\ fix}$	± 5 minutes
	4 minutes after $T_{0\ fix}$	± 2 minutes
	10 minutes after $T_{0\ fix}$	± 2 minutes
	15 minutes after $T_{0\ fix}$	± 2 minutes
	30 minutes after $T_{0\ fix}$	± 5 minutes
	1 hour after $T_{0\ fix}$	± 10 minutes
	2 hours after $T_{0\ fix}$	± 10 minutes
	4 hours after $T_{0\ fix}$	± 10 minutes

Table 16 Definition of Assessment Windows

Assessment	Nominal Time point(s) (relative to $T_{0\ fix}$ or $T_{0\ ad\ lib}$)	Window
	15 minutes prior to $T_{0\ ad\ lib}$	± 5 minutes
	10 minutes after $T_{0\ ad\ lib}$	± 2 minutes
	20 minutes after $T_{0\ ad\ lib}$	± 2 minutes
	30 minutes after $T_{0\ ad\ lib}$	± 5 minutes
	40 minutes after $T_{0\ ad\ lib}$	± 5 minutes
	1 hour after $T_{0\ ad\ lib}$	± 10 minutes
	2 hours after $T_{0\ ad\ lib}$	± 10 minutes
	4 hours after $T_{0\ ad\ lib}$	± 10 minutes
Adapted mCEQ	On Day 1, 2, 3 and 4	Within 60 minutes after the end of *ad libitum* product use
Sensory Questionnaire	On Day 1, 2, 3 and 4	Within 60 minutes after the end of *ad libitum* product use
Cough Assessment	On Day -1 prior to product test	
	24 hours after $T_{0\ fix}$ for each variant (performed on Day 2, 3, 4 and 5)	±1 hour
Vital Signs	Screening	Not applicable
	Day -1	Not applicable
	Pre fixed puffing on Day 1, 2, 3 and 4	Within 1 hour prior to product use
	60 minutes post fixed puffing on Day 1, 2, 3 and 4	± 10 minutes
	60 minutes after the end of *ad libitum* product use on Day 1, 2, 3 and 4	± 10 minutes
	Day 5	Not applicable
	Early Termination	Not applicable

(*) Applicable only at Day 5

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Data analysis will be performed using SAS® Version 9.2 or higher.

Nicotine PK parameters will be derived from plasma nicotine concentrations versus time data by non-compartmental analysis (NCA) and any required data transformation for the PK analysis on the provided analysis PK set will be conducted using Phoenix® WinNonlin® version 7.0 or higher (Certara L.P. (Pharsight), St. Louis, MO).

Data listings will be provided for all data collected as required by the protocol, and including all data derived for analysis purposes, ordered by subject, product variant (if applicable), use regimen (if applicable) and time point (if applicable), unless otherwise stated. Data listings will include all subject level data collected unless otherwise specified.

Summary statistics and statistical analysis will only be presented for data where detailed in this SAP.

Safety data will be summarized for the Safety Population. All endpoints other than safety will be analyzed using the PK population.

12.1.1 Stratified Presentation

Stratified by sex presentations will be conducted on the PK population for the following endpoints:

- Demographics
- Nicotine concentrations in blood
- PK parameters

12.1.2 Subgroup Analyses

No subgroup analyses will be performed in this study.

12.1.3 Descriptive Statistics

For continuous data, summary statistics will include the number (n) of subjects, the number and percent of subjects with missing data, the arithmetic mean and standard deviation (mean and SD), median, first and third quartiles, minimum and maximum.

For log-normal data (e.g., the PK parameters: AUC and C_{max}) the geometric mean and geometric CV will be used for interpretation and presented in addition to the arithmetic mean and SD.

For nicotine plasma concentrations, the number and percent of BLOQ samples, the geometric mean, the geometric CV and the 95% confidence interval of geometric mean will be presented in addition.

For categorical data, frequency counts and percentages will be presented.

For the calculation of summary statistics and statistical analysis, unrounded data will be used. However rounding will be performed for the presentation of final results as follows:

- For discrete or continuous data, data will be presentd rounded to 3 significant digits when below 1000; and they will be reported with all significant digits apart from the decimal digits when above or equal 1000. Summary statistics below

0.0001 will be displayed as 0. The geometric coefficient of variation (CV) will be reported as % with two decimal digits.

- For categorical data, frequency counts and percentages will be presented, missing values will be regarded as an own category if any missing value exists. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts.

All analyses and summaries will be performed by product and overall, and separately for fixed and *ad libitum* use regimen when applicable.

Unless otherewise speficied, summaries will be presented at Baseline and at each post baseline timepoint, including the change from baseline (calculated as difference from baseline).

12.1.4 Definitions for Statistical Data Analysis

Definitions for statistical analyses/presentations are detailed in Section 4.1 "Definitions for Statistical Analysis".

12.1.5 Handling of Dropouts or Missing Data (including outside the limits of quantitation)

For the derivation of PK parameters:

- Any missing value for baseline concentration (for both fixed regimen and *ad libitum* use) will be considered as 0 while no imputation will be performed for missing concentration values for all other endpoints.
- Values below the lower limit of quantitation (BLOQ) will be set to missing and ignored apart from:
  - BLOQ values before $T_{0\ fix}$ or $T_{0\ ad\ lib}$ are considered as zero. The same rule will be applied for each individual plasma concentration value between $T_{0\ fix}$ (respectively $T_{0\ ad\ lib}$) and the first time point above LLOQ.
  - BLOQ values after the last quantifiable value are not included in the analysis.
  - Any other BLOQ value (after $T_{0\ fix}$ or $T_{0\ ad\ lib}$ and before the last quantifiable value) would need to be queried and, if confirmed, it will be imputed by LLOQ/2. Otherwise the value will not be included in the analysis.

For the summary and the figures of nicotine concentration and laboratory parameters values:

- No imputation will be performed for missing concentration, summaries will be perfomed on available data.
- BLOQ values after $T_{0\ fix}$ or $T_{0\ ad\ lib}$ and before the last quantifiable value would need to be queried and, if not confirmed, it will be excluded from summary and figures. Other BLOQ values will be imputed by LLOQ/2.
- For values above the upper limit of quantitation (ULOQ), i.e. preceded by a ">", for example ">xx," the numerical xx will be used.

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

For CYP2A6 activity, any values BLOQ or above the ULOQ in the denominator will not be imputed and the derived variable will be presented as "Not Calculated" in descriptive summaries.

Questionnaire data total scores and domain or subscale scores may use a certain degree of imputation (by averaging across individual item scores) as detailed in Section 7.3 "Questionnaires". For assessment of cough, if no cough was reported at a given visit then the VAS score is imputed with zero.

If an actual sampling time or $T_{0\ fix}$ or $T_{0\ ad\ lib}$ is missing from the dataset, the corresponding nominal sampling time will be used instead.

If time of discharge is missing, then it will be imputed by 8pm of the day the subject was discharged.

Partial dates will not be imputed, but assumptions will be made as follows to assign to either medical history or concomitant diseases (Table 17), to assign to either product-emergent or non-product emergent adverse events (Table 18) and to assign to either prior or concomitant medications (Table 19):

Table 17 Partial Dates for Medical History or Concomitant Diseases

Date information	Assign as
Missing stop date	Concomitant disease
Partial date, e.g. --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of Screening.	Concomitant disease
Partial date, e.g. --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening.	Medical history

Table 18 Partial Dates for Adverse Events

Date information	Assign as
Partial date, e.g. --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of Visit 2	Product-emergent
Partial date, e.g. --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Visit 2.	Not product-emergent

Table 19 Partial Dates for Prior and Concomitant Medications

Date information	Assign as
Missing stop date	Concomitant
Partial date, e.g., --May2012, or -----2011. If month/year is the same as, or later than the month and/or year of Screening.	Concomitant
Partial date, e.g., --May2012, or -----2011. If month and/or year is earlier than the month and/or year of Screening.	Prior

12.1.5.1 Insufficient Data for Analysis/Presentation

If there are no values/event at the general value then the break out should not be presented. For example if the number of related AEs is zero then no presentation by severity of related events at the single level will be produced.

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the table, such as, "No serious adverse events occurred for this study."

Summaries will be limited when there are less than 4 assessments available for analysis, and only the number and percent of subjects available (by strata if applicable) and non-parametric summaries (min, max, median, quartiles) if applicable, will be presented.

12.1.6 Handling of Unplanned Data

Unscheduled post-product use assessments will be excluded from the summary statistics and only included in listings. Unscheduled assessments will be labelled as unscheduled in the listings and mapped to the study day using the date of the study day until midnight.

12.1.7 Significance Level for Inferential Analysis

This study has no formal pre-specified hypotheses associated with the study objectives.

Unless stated otherwise, all quoted confidence intervals are two-sided 95% confidence intevals (CI)

12.1.8 Multiple Comparisons/Multiplicity

No formal adjustment of the test-wise alpha level for multiple testing is necessary, as this study is descriptive in nature and no claim will be made based on the outcome of the individual CI values.

12.2 Disposition of Subjects

The number and percent of subjects will be summarized for the following categories (Table 15.2.1.1):

- screen failures (including reasons for screen failure);

- enrolled subjects;
  - enrolled subjects exposed;
  - enrolled subjects who discontinued before randomization and exposed (including reasons for not randomizing)
  - enrolled subjects who discontinued before randomization and not exposed (including reasons for not randomizing);
  - enrolled subjects who completed the safety follow-up;
- randomized subjects;
  - randomized subjects who completed;
  - randomized subjects who discontinued (including reasons for discontinuation);
  - randomized subjects who completed the safety follow-up.

The number and percent of subjects included into the analysis populations will be summarized as follows (Table 15.2.1.1.1):

- screened population;
- enrolled population;
- safety population;
- randomized population;
- PK population;
- randomized subjects excluded from PK population;
  - reasons for exclusion from the PK population.

Unmet inclusion and exclusion criteria will be listed for each screened subjects having any unmet criterion (Listings 15.3.1.1).

Supportive listings on subjects' disposition will be provided (Listings 15.3.1.1, 15.3.1.2.1, 15.3.1.2.2, 15.3.1.3). A listing of randomization schemes and codes will also be provided (Listing 16.1.7).

The number and percent of subjects with protocol deviations, and the number of protocol deviations, will be summarized (Listing 15.3.1.4; Table 15.2.1.2). Summaries will be broken down by main deviation category (major/minor), sub-categories, and evaluability impact . Subjects will be counted once per deviation category, and can be counted for more than one deviation category.

12.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the PK population, and listed for all screened subjects. This summary will also be performed for the safety population.

Summaries will include sex, age, race, height, weight and BMI, smoking history, FTND and cytochrome P450 2A6 (CYP2A6) activity. Demographics will be presented by sex as specified in Section 12.1.1 "Stratified Presentation".

No inferential analyses will be presented for the demographic and baseline characteristics.

12.3.1 Demographics

Sex, age, race, height, weight and BMI will be listed and summarized as specified in Section 12.3 "Demographics and Other Baseline Characteristics" (Listing 15.3.1.5, Tables 15.2.1.3.1, 15.2.1.3.1.1 and 15.2.1.3.2)

12.3.2 Smoking History and Habits

The following smoking characteristics at Screening will be listed and summarized as specified in Section 12.3 "Demographics and Other Baseline Characteristics" (Listing 15.3.1.6, Tables 15.2.1.3.1, 15.2.1.3.1.1 and 15.2.1.3.2):

- Smokers for at least the past 3 consecutive years
- Number of years the subjects have smoked
- Average cigarettes per day since smoking start
- Average cigarettes per day over the past four weeks
- Average menthol cigarettes per day over the past four weeks
- Brand of cigarettes (listed only)

12.3.3 FTND Questionnaire at Screening

FTND score value and the number and percentage of subjects in each category (mild/moderate/severe) will be presented. Data will be listed and summarized as reported in Section 12.3 "Demographics and Other Baseline Characteristics" (Listing 15.3.1.7, Tables 15.2.1.3.1, 15.2.1.3.1.1 and 15.2.1.3.2).

12.3.4 CYP2A6 Activity at Admission

CYP2A6 activity will be calculated as the metabolic ratio of trans 3' hydroxycotinine and cotinine measured at Admission (Day -1), as described in Section 7.2.1 "CYP2A6". Data will be listed and summarized as reported in section 12.3 "Demographics and Other Baseline Characteristics" (Listing 15.3.1.8, Tables 15.2.1.5.1, 15.2.1.5.1.1 and 15.2.1.5.2).

12.3.5 Medical History and Concomitant Diseases

Medical history is defined as any condition that started and ended prior to the ICF signature at Screening. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1, listed and summarized by System Organ Class (SOC) and Preferred Term (PT) within SOC. The number and percent of subjects with medical history diseases, and the number of medical history diseases, will be summarized (Listing 15.3.1.9, Table 15.2.1.3.3).

Concomitant disease is defined as any condition diagnosed at Screening or was ongoing at Screening. Concomitant disease will be coded using MedDRA version 20.1, listed and summarized by SOC and PT within SOC. The number and percent of subjects with concomitant diseases, and the number of concomitant diseases, will be summarized (Listing 15.3.1.9, Table 15.2.1.3.4).

12.3.6 Other Data

Other data collected at Screening and/or Admission will be listed by subject (Listing 15.3.1.10). These data are as follows:

- Serology for HIV and Hepatitis B and C (Screening)
- Urine cotinine test (Screening)
- Urine pregnancy test (Screening, Day -1, Day 5, Early Termination and Unscheduled assessments)
- Urine drug screen (Screening, Day -1)
- Alcohol breath test (Screening, Day -1 and Unscheduled assessments)

12.4 Measurements of Product Compliance

Non compliance to product allocation will be tracked by protocol deviations and summarized as described in Section 12.2 "Disposition of Subjects".

12.5 Extent of Exposure (Product Consumption)

Details of the product test and product use with all products will be listed. The number and percentage of subjects using 1, 2 or 3 P3P 3 products at product test, the number of puffs and duration of product use during the fixed puffing regimen and the number of products used and the total duration of product use during the ab libitum use (calculated as the sum of the durations of each product use) will be summarized per product variant for PK population and Safety (Listing 15.3.2.1, Tables 15.2.2.1 and 15.2.2.2).

12.6 Planned Statistical Analyses

12.6.1 Primary Analyses

Background-corrected and uncorrected Nicotine concentrations and PK parameters will be derived as described in Section 7.1 "Pharmacokinetic Parameters".

Background-corrected and uncorrected PK parameters cC_{max}, $cAUC_{fix(0\text{-}4h)}$, ct_{max}, C_{max}, $AUC_{fix(0\text{-}4h)}$ and t_{max} for fixed puffing regimen will be summarized by P3P variant.

The individual plasma nicotine concentrations over time and PK parameters will be summarized by P3P variant as detailed in section 12.1.3 "Descriptive Statistics" and will be presented by sex as described in Section 12.1.1 "Stratified Presentation" (Tables 15.2.3.1 and 15.2.3.1.1 for background-corrected concentrations, Tables 15.2.3.2 and

15.2.3.2.1 for uncorrected concentrations, Tables 15.2.3.3 and 15.2.3.3.1 for background-corrected PK parameters, Tables 15.2.3.4 and 15.2.3.4.1 for uncorrected PK parameters).

The individual uncorrected and background-corrected plasma nicotine concentrations and actual sampling times will be listed (Listing 15.3.3.1).

The individual uncorrected and background-corrected PK parameters will be listed (Listing 15.3.3.2).

The individual plasma nicotine concentrations up to 4 hours will be plotted by P3P variant in a linear and semi-logarithmic scale (Figures 15.1.3.1 and 15.1.3.2 for background-corrected concentrations, Figures 15.1.3.3 and 15.1.3.4 for uncorrected concentrations).

The geometric mean plasma nicotine concentrations up to 4 hours will be plotted by P3P variant and their 95% CI (Figures 15.1.3.5 and 15.1.3.6 for background-corrected concentrations, Figures 15.1.3.7 and 15.1.3.8 for uncorrected concentrations).

Boxplots of cC_{max}, $cAUC_{fix(0-4h)}$, C_{max} and $AUC_{fix(0-4h)}$ by P3P variant will be presented (Figure 15.1.3.9- 15.1.3.12).

A mixed model will be conducted on logarithmically transformed PK parameters for cC_{max}, $cAUC_{fix(0-4h)}$, C_{max} and $AUC_{fix(0-4h)}$ with fixed terms for sequence, product variant and two dummy variables for Day 3 and Day 4 (i.e two variables taking value 1 for Day 3 and Day 4 respectively and value 0 for the other study days) and using subject nested within sequence as random effect. In this way Day 1 and Day 2 will be combined to address the multicollinearity as planned in the protocol. The SAS code to be used is shown below:

```
proc mixed data=_data_;
   class Sequence Product_Variant Day3 Day4 Subject;
   model logPK_Parameter = Sequence Product_Variant Day3 Day4 / ddfm=SAT s;
   random Subject(Sequence) / sub=Subject type=CSH;
   lsmeans Product_Variant / cl diff alpha=0.05;
run;
```

In case of model convergence issues, this will be reported in the study report and the variance component (type=VC) covariance structure will be investigated.

Geometric least square means and ratios will be presented for the analysis of cC_{max}, $cAUC_{fix(0-4h)}$, C_{max} and $AUC_{fix(0-4h)}$ together with 95% CI by sex and overall for the following effects of interest (Tables 15.2.3.5, 15.2.3.5.1, 15.2.3.6 and 15.2.3.6.1):

- P3P 2 vs P3P 3, to describe the effect of a decrease of nicotine powder concentration from 2 mg to 1 mg.
- P3P 2 vs P3P 4, to describe the effect of a decrease from 2.25 μm to 1.8 μm of the median particle size in the nicotine powder
- P3P 2 vs P3P 1, to describe the effect of flavor

A sensitivity analysis will be conducted on C_{max}, cC_{max}, AUC and cAUC by including the study day in the model and restricting the analysis to P3P 1, 2 and 4 at study Days 2, 3 and 4 (Tables 15.2.3.5.2 and 15.2.3.6.2)

The analysis of t_{max} and ct_{max} will be performed by calculating the median t_{max} and ct_{max} for each P3P variant and the median difference between the P3P variants for the effect of interest mentioned above along with the Hodges-Lehmann (***Hodges and Lehmann, 1963***) 95% CI estimates (Tables 15.2.3.7 and 15.2.3.7.1 for stratified presentation).

All figures, summaries, and analysis will be produced for the PK population.

12.6.2 Secondary Analyses

12.6.2.1 Pharmacokinetics

The same approach as for the Section 12.6.1 "Primary Analyses" will be conducted for the following background-corrected and uncorrected secondary PK parameters for *ad libitum* use: cC_{peak}, cC_{trough}, $cC_{average}$, $cAUC_{ad\ lib\ (0\text{-}4h)}$, ct_{peak}, C_{peak}, C_{trough}, $C_{average}$, $AUC_{ad\ lib\ (0\text{-}4h)}$ and t_{peak}.

Background-corrected and uncorrected PK parameters for *ad libitum* use will be summarized by P3P variant.

The individual plasma nicotine concentrations over time and PK parameters will be summarized by P3P variant as detailed in section 12.1.3 "Descriptive Statistics" and will be presented by sex as described in Section 12.1.1 "Stratified Presentation" (Tables 15.2.3.8 and 15.2.3.8.1 for background-corrected concentrations, Tables 15.2.3.9 and 15.2.3.9.1 for uncorrected concentrations, Tables 15.2.3.10 and 15.2.3.10.1 for background-corrected PK parameters, Tables 15.2.3.11 and 15.2.3.11.1 for uncorrected PK parameters).

The individual uncorrected and background-corrected plasma nicotine concentrations and actual sampling times will be listed (Listing 15.3.3.3).

The individual uncorrected and background-corrected PK parameters will be listed (Listing 15.3.3.4).

The individual plasma nicotine concentrations over time will be plotted up to 4 hours by P3P variant in a linear and semi-logarithmic scale (Figures 15.1.3.13 and 15.1.3.14 for background-corrected concentrations, Figures 15.1.3.15 and 15.1.3.16 for uncorrected concentrations).

The geometric mean plasma nicotine concentrations over time will be plotted up to 4 hours by P3P variant and their 95% CI (Figures 15.1.3.17 and 15.1.3.18 for background-corrected concentrations, Figures 15.1.3.19 and 15.1.3.20 for uncorrected concentrations).

Boxplots of cC_{peak}, cC_{trough}, $cC_{average}$, $cAUC_{ad\ lib\ (0\text{-}4h)}$, C_{peak}, C_{trough}, $C_{average}$ and $AUC_{ad\ lib\ (0\text{-}4h)}$ by P3P variant will be presented (Figures 15.1.3.21-28).

Geometric least square means and ratios will be presented for the analysis of cC_{peak}, cC_{trough}, $cC_{average}$, $cAUC_{ad\ lib\ (0\text{-}4h)}$, C_{peak}, C_{trough}, $C_{average}$ and $AUC_{ad\ lib\ (0\text{-}4h)}$ together with 95% confidence interval by sex and overall for the following effects of interest (Table 15.2.3.12, Table 15.2.3.12.1, Table 15.2.3.13 and Table 15.2.3.13.1):

- P3P 2 vs P3P 3, to describe the effect of a decrease of nicotine powder concentration from 2 mg to 1 mg.

- P3P 2 vs P3P 4, to describe the effect of a decrease from 2.25 μm to 1.8 μm of the median particle size in the nicotine powder
- P3P 2 vs P3P 1, to describe the effect of flavor

A sensitivity analysis will be conducted on cC_{peak}, cC_{trough}, $cC_{average}$, $cAUC_{ad\ lib\ (0\text{-}4h)}$, C_{peak}, C_{trough}, $C_{average}$ and $AUC_{ad\ lib\ (0\text{-}4h)}$ by including the study day in the model and restricting the analysis to P3P 1, 2 and 4 at study Days 2, 3 and 4 (Tables 15.2.3.12.2 and 15.2.3.13.2).

The analysis of t_{peak} and ct_{peak} will be performed by calculating the median t_{peak} and ct_{peak} for each P3P variant and the median difference between the P3P variants for the effect of interest mentioned above along with the Hodges-Lehmann (***Hodges and Lehmann, 1963***) 95% CI estimates (Table 15.2.3.14 and Table 15.2.3.14.1 for stratified presentation).

12.6.2.2 Questionnaires

12.6.2.2.1 Visual Analogue Scale for Craving

The values of VAS for Craving and changes from baseline for fixed puffing regimen will be summarized by P3P variant and time point (Table 15.2.4.1) and listed (Listing 15.3.4.1). Individual profiles and profiles of the raw means will be produced by P3P variant and time point (Figures 15.1.4.1, 15.1.4.2).

A mixed model will be conducted for the values of VAS for Craving for fixed puffing regimen with fixed terms for sequence, product variant, two dummy variables for Day 3 and Day 4 (i.e two variables taking value 1 for Day 3 and Day 4 respectively and value 0 for the other study days), baseline value prior to product use, the time point and the interaction of product variant and time point and using subject nested within sequence as a random effect including the assessment timepoints as repeated measurements. In this way Day 1 and Day 2 will be combined to address the multicollinearity as planned in the protocol. The SAS code to be used is shown below:

```
proc mixed data=_data_;
   class Sequence Product_Variant Day3 Day4 Time_Point Subject;
   model VAS = Sequence Product_Variant Day3 Day4 VAS_Baseline
   Product_Variant*Time_Point / ddfm=SAT s;
   repeated Time_Point / subject=Subject type=CSH;
   random Subject(Sequence) / sub=Subject type=CSH;
   lsmeans Product_Variant / cl diff alpha=0.05;
   lsmeans Product_Variant*Time_Point / slice=Time_Point alpha=0.05 diff cl;
run;
```

In case of model convergence issues, this will be reported in the study report and the variance component (type=VC) covariance structure will be investigated.

Least square means and differences will be presented for the analysis of the values of VAS for Craving together with 95% confidence interval for the following effects of interest (Table 15.2.4.2):

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

The values of $AUC_{VAS\ fix\ (0\text{-}4h)}$ will be summarized by P3P variant (Table 15.2.4.3) and listed (Listing 15.3.4.2). Boxplot of $AUC_{VAS\ fix\ (0\text{-}4h)}$ by P3P variant will be presented (Figure 15.1.4.3).

A mixed model will be conducted for the values of $AUC_{VAS\ fix\ (0\text{-}4h)}$ for fixed puffing regimen with fixed terms for sequence, product variant and two dummy variables for Day 3 and Day 4 (i.e two variables taking value 1 for Day 3 and Day 4 respectively and value 0 for the other study days) and using subject nested within sequence as random effect. In this way Day 1 and Day 2 will be combined to address the multicollinearity as planned in the protocol. The SAS code to be used is shown below:

```
proc mixed data=_data_;
   class Sequence Product_Variant Day3 Day4 Subject;
   model AUC_VAS fix (0-4h) = Sequence Product_Variant Day3 Day4 / ddfm=SAT s;
   random Subject(Sequence) / sub=Subject type=CSH;
   lsmeans Product_Variant / cl diff alpha=0.05;
run;
```

In case of model convergence issues, this will be reported in the study report and the variance component (type=VC) covariance structure will be investigated.

Least square means and differences will be presented for the analysis of $AUC_{VAS\ fix\ (0\text{-}4h)}$ together with 95% confidence interval for the following effects of interest (Table 15.2.4.4):

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

The values of VAS for Craving and changes from baseline for *ad libitum* use will be summarized by P3P variant and time point (Table 15.2.4.5) and listed (Listing 15.3.4.3). Individual profiles and profiles of the raw means will be produced by P3P variant and time point (Figures 15.1.4.4 and 15.1.4.5).

The same mixed model as for fixed puffing regimen will be conducted for the values of VAS for Craving for *ad libitum* use. Least square means and differences will be presented for the analysis of the values of VAS for Craving for *ad libitum* use together with 95% confidence interval for the same effects of interest of VAS for Craving for fixed puffing regimen (Table 15.2.4.6).

The values of $AUC_{VAS\ ad\ libitum\ (0\text{-}4h)}$ will be summarized by P3P variant (Table 15.2.4.7) and listed (Listing 15.3.4.4). Boxplot of $AUC_{VAS\ ad\ libitum\ (0\text{-}4h)}$ by P3P variant will be presented (Figure 15.1.4.6).

The same mixed model as for fixed puffing regimen will be conducted for the values of $AUC_{VAS\ ad\ libitum\ (0\text{-}4h)}$ for *ad libitum* use. Least square means and differences will be presented for the analysis of $AUC_{VAS\ ad\ libitum\ (0\text{-}4h)}$ together with 95% confidence interval for the same effects of interest of $AUC_{VAS\ fix\ (0\text{-}4h)}$ for fixed puffing regimen (Table 15.2.4.8).

12.6.2.2.2 Adapted Modified Cigarette Evaluation Questionnaire

The adapted mCEQ subscale scores will be summarized by P3P variant (Table 15.2.4.9). The answers to the individual questions along with the scores will also be listed (Listing 15.3.4.5). Boxplot of adapted mCEQ subscale scores by P3P variant will be presented (Figure 15.1.4.7).

A mixed model will be conducted for the adapted mCEQ subscale scores with fixed terms for sequence, product variant and two dummy variables for Day 3 and Day 4 (i.e two variables taking value 1 for Day 3 and Day 4 respectively and value 0 for the other study days) and using subject nested within sequence as random effect. In this way Day 1 and Day 2 will be combined to address the multicollinearity as planned in the protocol. The SAS code to be used is shown below:

```
proc mixed data=_data_;
   class Sequence Product_Variant Day3 Day4 Subject;
   model mCEQ_Subscale_Score = Sequence Product_Variant Day3 Day4 / ddfm=SAT s;
   random Subject(Sequence) / sub=Subject type=CSH;
   lsmeans Product_Variant / cl diff alpha=0.05;
run;
```

In case of model convergence issues, this will be reported in the study report and the variance component (type=VC) covariance structure will be investigated.

Least square means and differences will be presented for the analysis of the adapted mCEQ subscale scores together with 95% confidence interval for the following effects of interest (Table 15.2.4.10):

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

12.6.2.2.3 Sensory Questionnaire

The sensory questionnaire scores of the individual questions will be summarized by P3P variant (Table 15.2.4.11). The answers to the individual questions along with the scores

will also be listed (Listing 15.3.4.6). Boxplot of sensory questionnaire scores of the individual questions by P3P variant will be presented (Figure 15.1.4.8).

A mixed model will be conducted for the sensory questionnaire scores with fixed terms for sequence, product variant and two dummy variables for Day 3 and Day 4 (i.e two variables taking value 1 for Day 3 and Day 4 respectively and value 0 for the other study days) and using subject nested within sequence as random effect. In this way Day 1 and Day 2 will be combined to address the multicollinearity as planned in the protocol. The SAS code to be used is shown below:

```
proc mixed data=_data_;
   class Sequence Product_Variant Day3 Day4 Subject;
   model SQ_Score = Sequence Product_Variant Day3 Day4 / ddfm=SAT s;
   random Subject(Sequence) / sub=Subject type=CSH;
   lsmeans Product_Variant / cl diff alpha=0.05;
run;
```

In case of model convergence issues, this will be reported in the study report and the variance component (type=VC) covariance structure will be investigated.

Least square means and differences will be presented for the analysis of the sensory questionnaire scores together with 95% confidence interval for the following effects of interest (Table 15.2.4.12):

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

12.6.3 Human Puffing Topography

Human Puffing Topography parameters per puff and per product use experience will be listed for fixed puffing regimen and *ad libitum* use (Listing 15.3.4.7, Listing 15.3.4.8, Listing 15.3.4.9 and Listing 15.3.4.10).

Human Puffing Topography parameters per puff and per product use experience will be summarized by P3P variant for fixed puffing regimen and *ad libitum* use with geometric mean, CV, arithmetic means, SD and 95% CIs (Table 15.2.4.13, Table 15.2.4.14, Table 15.2.4.15 and Table 15.2.4.16).

12.6.4 Weight difference of P3P before and after use

The values of weight before and after use and their differences will be listed for fixed puffing regimen and *ad libitum* use (Listing 15.3.4.11 and Listing 15.3.4.12) and summarized by P3P variant for fixed puffing regimen and *ad libitum* use (Table 15.2.4.17 and Table 15.2.4.18).

12.6.5 Safety Evaluation

Safety variables monitored in this study include: AEs; vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); spirometry; ECG data; concomitant medication, clinical chemistry, hematology, urine analysis safety panel, BMI, physical examination, respiratory symptoms (cough assessment).

The primary analysis of Safety parameters will be conducted on the Safety population as described in Section 12.1.3 "Descriptive Statistics".

12.6.5.1 Safety Reporting

Safety data will be tabulated on the safety population by exposure period defined as:

- Pre-dose Period: Prior to any Product Use [ICF , first use of P3P 3 test at Day-1[. According to protocol, first use would be P3P 3 product test at Day-1.
- Product Test Period: [First use of P3P 3 test at Day-1, First use of P3P 3 at Day 1[
- P3P 3 Period: [First use of P3P 3 at Day 1, First use of product at Day 2 or time of discharge[
- P3P 1 Period: [First use of P3P 1, First use of the next product variant or time of discharge[
- P3P 2 Period: [First use of P3P 2, First use of the next product variant or time of discharge[
- P3P 4 Period: [First use of P3P 4, First use of the next product variant or time of discharge[
- Safety Follow-Up Period : [from time of discharge, 7 days after discharge].

Safety data will be assigned to the specific safety period where the collection time or start time of the AE is included between beginning and the end of the period.

All AEs occurring from the time of signing of informed consent will be recorded and listed.

Only product emergent AEs will be summarized (the ones occurring during pre-dose period will be listed only). If an AE occurs during the Safety follow up period, then this AE will not be assigned to the last product used but summarized in the Safety Follow-Up Period.

A product emergent AE is defined as an AE that occurs after first P3P product use or that is present prior to first product use and becomes more severe after first product use. All other AEs will not be summarized but provided in listings only.

12.6.5.2 Adverse Events

All AE will be listed (Listing 15.3.6.1.1) and summarized by exposure period and overall:

- The number of events and the number and percentage of subjects reporting at least one AE (Table 15.2.6.1);

- The number of serious/non serious events and the number and percentage of subjects reporting at least one serious/non serious AE (Table 15.2.6.1);
- If applicable, the number of events and the number and percentage of subjects reporting at least one SAE classified by reason for seriousness (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one AE broken down by product relatedness (related, not related) (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one AE broken down by study procedure relatedness (related, not related) (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one AE broken down by expectedness (expected, not expected) (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one AE broken down by severity, including a subject once with worst severity (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one AE broken down by action taken related to the product (combining the following items: product use interrupted, product use reduced, product use stopped) and other action taken (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one AE leading to product discontinuation (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one AE leading to study discontinuation (Table 15.2.6.1);
- The number of events and the number and percentage of subjects reporting at least one SAE leading to death (Table 15.2.6.1).

Additional summary tables of AEs will be presented with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by SOC and PT coded according to the MedDRA dictionary (version 20.1):

- The number of events and the number and percentage of subjects reporting at least one AE (Table 15.2.6.2);
- The number of frequent events (i.e. the events with an incidence - calculated as number of subjects reporting the event divided the number of subject included in the safety population - greater than 5%) and the number and percentage of subjects reporting at least one frequent AE (Table 15.2.6.2.1);
- The number of events and the number and percentage of subjects with at least one AE related to study product (Table 15.2.6.3);
- The number of events and the number and percentage of subjects with at least one AE related to study procedures (Table 15.2.6.4);
- The number of events and the number and percentage of subjects with at least one expected AE (Table 15.2.6.5);
- The number of events and the number and percentage of subjects with at least one AE by severity (mild, moderate, severe) (Table 15.2.6.6);

- The number of events and the number and percentage of subjects with at least one AE leading to product discontinuation (Table 15.2.6.7);
- The number of events and the number and percentage of subjects with at least one AE leading to study discontinuation (Table 15.2.6.8);

If a subject has more than one occurrence of the same AE, the subject will be counted only once within a PT for each sequence, with the worst occurrence based on the presentation (e.g., for presentation by severity = most severe, for presentation by relationship = most related). Missing information on the intensity of AE will be counted as severe.

12.6.5.2.1 Serious Adverse Events (Including Deaths)

All SAE will be listed in a separate listing (Listing 15.3.6.1.2) and summarized as described in section 12.6.5.2 (Table 15.2.6.1).

12.6.5.2.2 Adverse Events Leading to Study Discontinuation

AEs leading to study discontinuation will be listed in a separate listing (Listing 15.3.6.1.3) and summarized as described in section 12.6.5.2 (Table 15.2.6.1).

12.6.5.3 P3P Product Events and Malfunctions

All events (product malfunction/misuse) related to the P3P will be listed for each subject, including event description, severity of event, AE relationship, action taken and onset/stop dates/times.

Product events will be listed (Listing 15.3.6.2) and summarized by exposure period and overall:

- Number of product events and the number and percentage of subjects reporting at least one product event (Table 15.2.6.9);
- Number of product events and the number and percentage of subjects categorized by severity of product event (minor, major) (Table 15.2.6.9);
- Number of product events and the number and percentage of subjects categorized by AE relationship (related, not related) (Table 15.2.6.9);

12.6.5.4 Clinical Laboratory Evaluation

Table 20 lists the hematology, clinical chemistry and urine analysis parameters to be assessed in this study.

Table 20 List of Laboratory Safety Parameters

Hematology	Clinical Chemistry	Urine Analysis
• Hematocrit • Hemoglobin • Mean corpuscular	• Albumin • Total protein • Alkaline phosphatase	• pH • Bilirubin • Glucose

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	• Alanine aminotransferase • Aspartate aminotransferase • Blood urea nitrogen • Creatinine • Gamma-glutamyl transferase • Fasting glucose* • Lactate dehydrogenase • Potassium • Sodium • Total bilirubin • Direct bilirubin • Total cholesterol • Triglycerides	• Nitrite • Red blood cell traces • Protein • Specific gravity

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

Any clinical safety laboratory test result will be reviewed by the Investigator and assessed for clinical significance.

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

The grading scheme used in the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [CTCAE] version 4.03) will be used by the Investigator to assess abnormal laboratory AEs. These CTCAE grades will be derived programmatically and are available in the SDTM laboratory dataset.

Laboratory actual values and changes from baseline will be listed and summarized at Screening, Baseline, and post product use by product variant for assessments performed at Day 2-5 or at time of discharge refering to product used at Day 1-4 (i.e. assessments performed on Day 2 are related to P3P 3 used on Day 1) (Listings 15.3.6.3, 15.3.6.4 and 15.3.6.5). The number and percentage of subjects with normal/abnormal not clinically significant/abnormal clinically significant results will be tabulated for laboratory parameters (Tables 15.2.6.10.1, 15.2.6.11.1 and 15.2.6.12.1).

Listings for the clinical laboratory data will include the following information: normal/high/low (with respect to the reference range) or normal/abnormal (with respect to the reference value), clinically significance (as defined by the Investigator), the change

from baseline and the CTCAE grade. Only CTCAE grades greater than zero will be presented.

Descriptive statistics will be presented for actual values and changes from baseline (Table 15.2.6.10.2, Table 15.2.6.11.2 and Table 15.2.6.12.2), tables of frequency will be presented for qualitative values (Table 15.2.6.12.3) and shift tables from baseline will be provided (Tables 15.2.6.10.3, 15.2.6.11.3, 15.2.6.12.4 and 15.2.6.12.5).

12.6.5.5 Vital Signs, Physical Findings and Other Observations Related to Safety

12.6.5.5.1 Prior and Concomitant Medication

Prior medication is defined as any medication that started and ended prior to Screening. Concomitant medication is defined as any medication starting on or after Screening. Medications that started prior to Screening and are ongoing at Screening are considered as concomitant.

All medications will be listed by P3P variant and exposure period using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization - Drug Dictionary Enhanced [WHO-DDE] September 2017 C format). A flag will be presented on the listing indicating whether the medication is prior or concomitant.

Prior and concomitant medications will be listed (Listing 15.3.6.6). Listing will display original dates (no imputation). Prior and concomitant medications will be summarized for the Safety population showing the number (%) of subjects who used the medication at least once by sequence and by ATC 1st and 2nd levels medical term and by preferred drug name (Tables 15.2.6.13.1, 15.2.6.13.2, 15.2.6.14.1 and 15.2.6.14.2).

12.6.5.5.2 Physical Examination

Physical examination data recorded at the Screening, Day -1, Day 5 or at early termination will be listed (Listing 15.3.6.7). Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged.

The number and percentage of subjects with normal, abnormal and abnormal clinically significant results will be tabulated by body systems at each recording time point (Table 15.2.6.15).

12.6.5.5.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate and respiratory rate) will be measured at Screening, Day -1 and on every day of confinement (from Day 1 to Day 5/early termination). From Day 1 to Day 4, vital signs will be assessed within 60 minutes prior to product use and 60 minutes ± 10 minutes after each product use period (fixed puffing regimen and *ad libitum* use). Every measurement of vital signs has to be assessed as normal or abnormal and, if abnormal, as clinically significant or not clinically significant. A diagnosis has to be provided in the CRF for all measurement of vital signs assessed as abnormal and clinically significant.

Vital signs values, changes from baseline (i.e. Day -1 or pre-fixed puffing measurement) and normality evaluation will be listed (Listing 15.3.6.8).

Descriptive statistics will be presented for values and changes from baseline and the number and percentage of subjects with normal/abnormal not clinically significant/abnormal clinically significant results will be reported by P3P variant and time point (Tables 15.2.6.16.1, 15.2.6.16.2, 15.2.6.16.3 and 15.2.6.16.4).

12.6.5.5.4 Spirometry

Spirometry parameters (FEV_1, FEV_1 % predicted, FVC, FVC % predicted, FEV_1/FVC) will be measured at Screening and Day 5 or early termination. Every measurement of spirometry parameters has to be assessed as normal or abnormal and, if abnormal, as clinically significant or not clinically significant. A diagnosis has to be provided in the CRF for all measurement of spirometry parameters assessed as abnormal and clinically significant.

Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set (**Hu and Cassano, 2000**).

Spirometry parameters, changes from baseline (i.e. screening) and normality evaluation will be listed (Listing 15.3.6.9).

Descriptive statistics will be presented for values and changes from baseline and the number and percentage of subjects with normal/abnormal not clinically significant/abnormal clinically significant results will be reported by time point (Tables 15.2.6.17.1 and 15.2.6.17.2).

12.6.5.5.5 Electrocardiogram

The ECG measurements will be obtained directly from the 12-lead ECG traces, i.e. not centrally read. These measurements (heart rate, PR interval, QRS duration, QT interval, QTcB interval, QTcF interval) will be measured at Screening, Day -1 and on every day of confinement (from Day 1 to Day 5/early termination). On Day 1 to Day 4, ECG will be assessed post fixed puffing regimen and post *ad libitum* use. Every measurement of ECG has to be assessed as normal or abnormal and, if abnormal, as clinically significant or not clinically significant. A diagnosis has to be provided in the CRF for all measurement of ECG assessed as abnormal and clinically significant.

ECG measurements, changes from baseline (i.e. Day -1) and normality evaluation will be listed (Listing 15.3.6.10).

Descriptive statistics will be presented for measurements and changes from baseline and the number and percentage of subjects with normal/abnormal not clinically significant/abnormal clinically significant results will be reported by P3P variant and time point (Tables 15.2.6.18.1, 15.2.6.18.2).

12.6.5.5.6 Assessment of Cough

Cough questionnaire is assessed on Day -1 prior to product test and prior to product use on Day 2, 3, 4 and 5. Questionnaire details are reported in Section 7.3.5 "Cough Assessment".

The answer to the Cough questionnaire will be listed (Listing 15.3.6.11).

The number and % of subjects reporting a cough will be summarized at baseline and after product use. The responses to the individual items, including the VAS evaluating the level of cough bother and 3 Likert scales mesuring the intensity, the frequency of cough and the amount of sputum production will be listed and summarized at baseline and change from baseline by P3P variant, for all subjects who filled in the questionnaire. The answers to the open question related to any other important observation will be listed only (Table 15.2.6.19).

13 ANALYSIS AND REPORTING

13.1 Interim Analysis and Data Monitoring

The interim PK analysis is being conducted with the main aim of evaluating whether the plasma nicotine concentration data are amenable to background-concentration correction via the Non-Compartmental Analysis (NCA) method, as described in the P3P-PK-01-CH study protocol and which is dependent on the estimation of the terminal elimination rate constant λz (see Section 13.1.3.1 "Primary PK Analysis Methodology (NCA-based method)" for further details). If plasma concentrations cannot be background-corrected in a sufficient number of subjects e.g., in the event that λ_z (or $t_{1/2z}$) cannot be estimated, alternative approaches will be evaluated including conventional Compartmental Analyses (CA) or population PK methods. These alternative PK analysis methods are also described in more detail in the following sub-sections.

A Clinical Research Associate ("Monitor") from [redacted] will be responsible for the monitoring of the study. Monitoring will be performed according to [redacted] standard operating procedures (SOPs) and as per the agreed monitoring plan with PMI.
The PI, or a designated member of the PI'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.

All changes to the source data will have to be approved by the PI.

13.1.1 Interim Analysis Objectives

The objective of this interim PK analysis is to select the methods that will enable the background-correction of nicotine concentrations for the purposes of accurately estimating PK parameters for each specific P3P variant and regimen by adjusting for possible carry-over effects due to limited wash-out periods between product use of different product use regimen or P3P variants.

Three different PK analysis methodologies will be evaluated sequentially, from simplest to most complex. More complex approaches will only be evaluated if the preceding simpler approach is deemed to be unsuccessful.

The evaluation will be performed sequentially in the following order:

- To evaluate whether the per protocol NCA plasma nicotine background-correction method can be used (this analysis methodology is described in Section 13.1.3.1 "Primary PK Analysis Methodology (NCA-based method)";
- To evaluate whether CA can be used to estimate the terminal elimination half-life of plasma nicotine to enable background-correction and subsequent estimation of PK parameters by NCA (see Section 13.1.3.2 "Alternative PK Analysis Methodology (CA-based method)";
- To evaluate if available plasma nicotine data is a priori amenable to background-correction via population PK methods (nonlinear mixed-effect modeling), see Section 13.1.3.3 "Population PK Analysis Methodology (Non-Linear Mixed Effects Modelling)".

13.1.2 Interim Analysis Materials

13.1.2.1 Bioanalytical Data

The interim analysis is to be performed on the quality controlled data, as provided by the bioanalytical laboratory, prior to database lock.

13.1.2.2 Analysis Dataset

The specifications of the PK analysis dataset will be described in a Data Transfer Agreement (DTA) that will be completed prior to the start of any interim PK analysis activities.

13.1.3 Interim Analysis Methods

The methods for PK parameters derivation are described in Section 7.1.2 "PK Parameters".

13.1.3.1 Primary PK Analysis Methodology (NCA-based method)

The nicotine terminal elimination rate constant λ_z (and $t_{1/2z}$) will be estimated as described in Section 7.1.2.3 "Criteria for Calculating the Apparent Terminal Elimination Half-Life" For the purposes of background-correction of the plasma concentrations post-baseline the following formula will be applied: $cC_t = C_t - C_0 \cdot e^{-\lambda z \cdot t}$. Where cC_t is the corrected concentration at each time point, C_t is the concentration at each time point, C_0 is the pre-use baseline concentration, λ_z is the terminal elimination rate constant and t is the actual time.

If the predicted cC_t is < 0.2 ng/mL (the bioanalytical LOQ threshold), this value will be used for the estimation of the background-corrected PK parameter (NCA analysis) only if the corresponding C_t is above LOQ, and the predicted cC_t will be imputed by zero if

negative. The derivation of cC_t from C_t values BLOQ will follow rules specified in section 12.1.5.

To evaluate the applicability of this background-correction method, the number of subjects for whom λ_z can be robustly estimated from the PK samples collected at Days 4 to 5 (see section 7.1.2.3 "Criteria for Calculating the Apparent Terminal Elimination Half-Life") will be considered, as this will limit the number of evaluable subjects for the background-corrected PK analysis.

If λ_z cannot be reliably estimated (see Section 7.1.2.3 "Criteria for Calculating the Apparent Terminal Elimination Half-Life") for a relevant number of subjects (e.g. for at least 80% of the PK population) then an alternative approach described in the next section will be evaluated.

13.1.3.2 Alternative PK Analysis Methodology (CA-based method)

Based on a visual examination of the concentration/time profiles, different potential compartmental PK models will be assessed. As a starting point, a two-compartment linear disposition combined with zero-order absorption model will be considered as this has previously been found to adequately describe the absorption phase and the biphasic disposition of plasma nicotine following administration via other smoking devices (***Marchand et al., 2017***).

For the purpose of this analysis the following assumptions in terms of nicotine exposure ("dose") will be made:

1. The nicotine content in the P3P capsule (1 or 2 mg) multiplied by the before and after use 'weight differential' ($\Delta W = W_{before} - W_{after}$) is directly proportional to the nicotine intake ([P3P capsule nicotine content × ΔW] $\propto$ nicotine exposure) and will be used as a surrogate 'dose' for the inhaled nicotine exposure (intake) for the purposes of modelling, for both fixed and ad libitum regimens.

2. For fixed regimens, duration of puffing and the Human Puffing Topography (HPT) parameters are the same in all study subjects.

3. The smoking start and stop time will be used as the nicotine intake duration. For any other occasions where the nicotine exposures or duration of smoking are unknown (e.g. Day -1) these will be estimated during the model fitting.

After successfully fitting the individual plasma nicotine data with a PK model, the same approach described in Section 13.1.3.1 will be adopted to derive corrected nicotine levels by means of subject-specific λ_z predicted by the model. General equations for determination of λ_z from the parameters estimated in a two-compartment model are presented below:

$$k_{10} = \frac{\mathrm{CL/F}}{V1/F}, k_{12} = \frac{\mathrm{CL/F}}{V1/F} \text{ and } k_{21} = \frac{\mathrm{CL/F}}{V1/F}$$

$$\lambda_1 = 0.5 \times (k_{12} + k_{21} + k_{10} + \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4 \times k_{21} \times k_{10}})$$

$$\lambda_2 (\equiv \lambda_z) = 0.5 \times (k_{12} + k_{21} + k_{10} - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4 \times k_{21} \times k_{10}})$$

CL/F: Apparent plasma nicotine clearance; Q/F: Apparent intercompartmental clearance; V1/F: Apparent volume of central compartment; V2/F: Apparent volume of peripheral compartment; λ_1: Initial rate constant; λ_2: Terminal rate constant (equivalent to λ_z); k_{10} micro elimination rate constant; k_{12} micro rate constant for the transfer from the central to the peripheral compartment;, k_{21}: micro rate constant for the transfer from the peripheral to the central compartment.

To evaluate the overall applicability of this background-correction method, the number of subjects with reliable λ_z will be evaluated as described in Section 13.1.3.1.

13.1.3.3 Population PK Analysis Methodology (Non-Linear Mixed Effects Modelling)

In the event that the two previously described PK analysis methods fail in background-correcting the data, a population PK analysis approach will be used.

This method will involve pooling the data from the present study with that of previous Philip Morris clinical studies and fitting this new dataset with the previously described population PK model by Marchand et al. (***Marchand et al., 2017***) to ultimately obtain the post hoc individual estimates of the PK parameters and the corresponding background-corrected individual PK parameters (C_{max}, $AUC_{(0\text{-}4h)}$) for subjects in study P3P-PK-01-CH.

Once individual parameters are obtained, PK simulations will be generated for each individual and P3P variant so as to obtain the corresponding background-corrected exposure PK parameters (e.g. cC_{max}, $cAUC_{fix\ (0\text{-}4h)}$, etc.).

Similar to the compartmental analysis method, an important caveat for its applicability is that it requires knowledge of the actual nicotine exposure after both fixed puffing as well as ad libitum regimens (i.e. a reasonably accurate data on the nicotine input into systemic circulation over time).

The data will be explored graphically to evaluate its a priori fitness for modeling via this method (e.g. missing data, completion of the PK profiles, outliers etc,). If a population PK analysis methodology is to be considered a stand alone Modeling Analysis Plan (MAP) will be written. Although the final decision on the method for nicotine adjustment should be taken before the database lock, the MAP may be finalized after db lock.

In case the population PK method is also deemed unsuccessful, only the uncorrected PK parameters will be reported and used for statistical analyses.

13.1.4 Interim PK Deliverables

The results of the Interim Analysis will be reported in an Interim Analysis Report that will be reviewed by the Sponsor.

This report will include a discussion on the evaluated background-correction methods and Certara recommendation as the best method to be taken for the final PK analysis following database lock. In addition, it will describe the results and provide Tables, Figures and Listings related to interim PK concentrations and/or parameters.

All the unadjusted PK parameters will be calculated for the interim analysis as described in Section 7.1.2 "PK Parameters".

The interim analysis report, will include the following figures:

- Individual and geometric mean (CV%) plasma nicotine concentration versus time profiles by product variant and product use regimen (linear and semi-log scales)
- Boxplots of PK exposure parameters (e.g. C_{max}, AUC) by product variant and product use regimen (fixed and ad libitum)
- Compartmental method only:
  - Goodness-of-fit/Diagnostic Plots
  - Individual PK model fits

The following summaries will also be provided:

- Geometric mean (CV%) unadjusted PK parameters for fixed and ad libitum regimens
  - Note: The background-corrected parameters will not be estimated during interim evaluations.
- Number of subjects with robustly estimated λ_z (or $t_{1/2z}$) for each of the evaluated background-correction methods (including the number of subjects for which λ_z could not be reliably estimated).
- For the compartmental method only (provided this method is evaluated and that there is sufficient data to apply a model-based approach):
  - Geometric mean (CV%) model-based estimated PK parameters (e.g. volume of distribution, clearance).

The following listings will also be provided:

- Listing of NCA-derived individual PK parameters
- Listing of the model compartmental analysis individual parameters (only if this methodology is evaluated).
- List of data excluded or imputed in the analysis

Full documentation of CA model fitting for final analysis will be provided in statistical output listing in the final study report including estimates of individual CA model parameters, model selection criteria and goodness of fit diagnostics (including, diagnostic plots and tabular summaries of Akaike information criterion and bayesian information criterion).

13.2 Interim QC Programming

Dry-run TFLs based on study data may be produced before DB lock for QC programming purposes.

13.3 Safety Reporting

Statistical summaries required for safety reporting will be made available to PMI medical safety officer following database lock. These summaries are flagged in the TFLs list reported in Appendix 16.2 "Tables, Figures and Listings".

13.4 Topline Results

Topline results, composed of key statistics and study results listings, will be made available to PMI management following database lock and prior to completion of the complete set of TFLs. The topline TFLs are listed in Appendix 16.2 "Tables, Figures and Listings".

13.5 Final Analyses

Final analyses for this study will be performed only after database lock. A pre-analysis data review meeting will be held prior to database lock and completion of the final analyses. In addition, no database may be locked, or analyses completed until the final version of this SAP has been approved.

Any post-hoc, additional exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as applicable. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

The list of all tables, figures and listings to be presented are included in the relevant sections of the SAP.

13.6 Clinical Trials.gov Reporting

Statistical summaries which will be evaluated for publishing on the Clinical trials.gov website (NCT02396381) are listed in Appendix 16.2 "Tables, Figures and Listings".

14 DATA PRESENTATION

Data presentation details are provided in a separate TFL mock shell document, based on the PMI style guide provided by PMI.

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16 APPENDICES

16.1 Study Assessments

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

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3	Day 4	Day 5 Discharge [q]	Day 5 to 12 Safety Follow-Up [o]
Prior medication [c]	●							
Concomitant medication	●	●	●	●	●	●	●	●
Physical examination	●	●					●	
Body height, weight and related BMI	●							
Vital signs [d]	●	●	●	●	●	●	●	
ECG [e]	●	●	●	●	●	●	●	
Spirometry	●						●	
Blood and urine sample collection for hematology, clinical chemistry, urine analysis safety panel [f]	●	●		●	●	●	●	
Blood sample collection for serology	●							
Urine drug screen	●	●						
Urine cotinine screen (dip stick)	●							
Alcohol breath test	●	●						
Urine Pregnancy test (females)	●	●					●	
trans-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma [g]			●					
FTND questionnaire	●							
Enrollment		●						

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3	Day 4	Day 5 Discharge [q]	Day 5 to 12 Safety Follow-Up [o]
P3P product test [h]		●						
Randomization [i]				●				
P3P product use. Fixed puffing in the morning with HPT followed by *ad libitum* use in the afternoon with HPT [j]			●	●	●	●		
Blood sample collection for plasma nicotine [k]			●	●	●	●	●	
VAS-craving [l]			●	●	●	●		
Adapted mCEQ [m]			●	●	●	●		
Sensory Questionnaire [m]			●	●	●	●		
Cough assessment [n]		●		●	●	●	●	
AE/SAE recording [o]	●	●	●	●	●	●	●	●
Product events Malfunctions/Misuse		●	●	●	●	●		
Support during periods of smoking abstinence (as required)			●	●	●	●	●	
Weighing of P3P products [p]			●	●	●	●		

See also instructions and abbreviations on the following page.

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

a. Prior to enrollment at Admission the following inclusion and exclusion criteria will be re-checked: Inclusion Criteria: Subject is not planning to quit smoking within 2 months, Subject is available during the study period and ready to comply with study procedures. Exclusion criteria: Subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in study, subject has a positive urine drug screen, subject uses estrogen containing medication, female subject who is pregnant or breast-feeding, female subject of childbearing potential who does not agree to use effective contraception. The following eligibility criteria will only be checked at Admission: subjects will not be included if they have received medication within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer) which has an impact on CYP2A6 activity.

b. Sex, date of birth, race.

c. All medication taken within 4 weeks prior to the Screening Visit will be documented. Prior medication which has an impact on CYP2A6 activity taken within 14 days or within 5 half-lives of the drug (whichever is longer) prior to Day -1 is an exclusion criteria.

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

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

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

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

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

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

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

60 minutes. Subjects will use P3P 3 at Day 1 and P3P 1, P3P 2 and P3P 4 in a randomized sequence at Days 2, 3 and 4.

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

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

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

l. The VAS craving will be completed by the subject at Days 1 to 4. For the fixed puffing regimen the first assessment will be done 15 minutes ± 5 minutes prior to T0 fix, all other assessments will be done after T0 fix, at 4 minutes ± 2 minutes, at 10 minutes ± 2 minutes, at 15 minutes ± 2 minutes, 30 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each. For the *ad libitum* use period the first assessment will be done 15 minutes ± 5 minutes prior to T0 ad lib, all other assessments will be done after T0 ad lib, at 10 minutes ± 2 minutes, at 20 minutes ± 2 minutes, 30 minutes ± 5 minutes, 40 minutes ± 5 minutes, 1 hour, 2 hours, 4 hours ± 10 minutes each.

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

n. VAS, three Likert scales and one open question. The cough questionnaire will be completed at Admission prior to product test and 24 hours (± 1 hour) after T0 fix for each variant (but prior to next variant use).

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

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

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

16.2 Tables, Figures and Listings

The table below reports all the TFLs and flags those required for topline review, safety reporting, and Clinical Trial.gov reporting.

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.1.1	Summary of Subject Disposition - Screened Population			
Table 15.2.1.2	Summary of Protocol Deviations - Safety Population			
Table 15.2.1.3.1	Descriptive Statistics of Demographics and Other Baseline Characteristics - PK Population	Y		Y
Table 15.2.1.3.1.1	Descriptive Statistics of Demographics and Other Baseline Characteristics by Sex - PK Population			
Table 15.2.1.3.2	Descriptive Statistics of Demographics and Other Baseline Characteristics - Safety Population		Y	
Table 15.2.1.3.3	Summary of Medical History - Safety Population		Y	
Table 15.2.1.3.4	Summary of Concomitant Diseases - Safety Population		Y	
Table 15.2.2.1	Descriptive Statistics of Product Use - PK Population			
Table 15.2.2.2	Descriptive Statistics of Product Use - Safety Population		Y	
Table 15.2.3.1	Descriptive Statistics of Background-Corrected Nicotine Plasma Concentrations following Fixed Puffing Regimen - PK Population	Y		

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.3.1.1	Descriptive Statistics of Background-Corrected Nicotine Plasma Concentrations following Fixed Puffing Regimen by Sex - PK Population			
Table 15.2.3.2	Descriptive Statistics of Uncorrected Nicotine Plasma Concentrations following Fixed Puffing Regimen - PK Population			
Table 15.2.3.2.1	Descriptive Statistics of Uncorrected Nicotine Plasma Concentrations following Fixed Puffing Regimen by Sex - PK Population			
Table 15.2.3.3	Descriptive Statistics of Background-Corrected Nicotine Plasma PK Parameters following Fixed Puffing Regimen - PK Population	Y		
Table 15.2.3.3.1	Descriptive Statistics of Background-Corrected Nicotine Plasma PK Parameters following Fixed Puffing Regimen by Sex - PK Population			
Table 15.2.3.4	Descriptive Statistics of Uncorrected Nicotine Plasma PK Parameters following Fixed Puffing Regimen - PK Population			
Table 15.2.3.4.1	Descriptive Statistics of Uncorrected Nicotine Plasma PK Parameters following Fixed Puffing Regimen by Sex - PK Population			
Table 15.2.3.5	Analysis of Background-Corrected Nicotine PK Parameters following Fixed Puffing Regimen - PK Population	Y		Y
Table 15.2.3.5.1	Analysis of Background-Corrected Nicotine PK Parameters following Fixed Puffing Regimen by Sex - PK Population			
Table 15.2.3.5.2	Analysis of Background-Corrected Nicotine PK Parameters following Fixed Puffing Regimen - Sensitivity analysis restricted to P3P 1, 2 and 4 - PK Population			

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.3.6	Analysis of Uncorrected Nicotine PK Parameters following Fixed Puffing Regimen - PK Population			
Table 15.2.3.6.1	Analysis of Uncorrected Nicotine PK Parameters following Fixed Puffing Regimen by Sex - PK Population			
Table 15.2.3.6.2	Analysis of Uncorrected Nicotine PK Parameters following Fixed Puffing Regimen - Sensitivity analysis restricted to P3P 1, 2 and 4 - PK Population			
Table 15.2.3.7	Analysis of Background-Corrected and Uncorrected Nicotine ctmax and tmax following Fixed Puffing Regimen - PK Population			
Table 15.2.3.7.1	Analysis of Background-Corrected and Uncorrected Nicotine ctmax and tmax following Fixed Puffing Regimen by Sex - PK Population			
Table 15.2.3.8	Descriptive Statistics of Background-Corrected Nicotine Plasma Concentrations following Ad Libitum Use - PK Population			
Table 15.2.3.8.1	Descriptive Statistics of Background-Corrected Nicotine Plasma Concentrations following Ad Libitum Use by Sex - PK Population			
Table 15.2.3.9	Descriptive Statistics of Uncorrected Nicotine Plasma Concentrations following Ad Libitum Use - PK Population			
Table 15.2.3.9.1	Descriptive Statistics of Uncorrected Nicotine Plasma Concentrations following Ad Libitum Use by Sex - PK Population			
Table 15.2.3.10	Descriptive Statistics of Background-Corrected Nicotine Plasma PK Parameters following Ad Libitum Use - PK Population			

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.3.10.1	Descriptive Statistics of Background-Corrected Nicotine Plasma PK Parameters following Ad Libitum Use by Sex - PK Population			
Table 15.2.3.11	Descriptive Statistics of Uncorrected Nicotine Plasma PK Parameters following Ad Libitum Use - PK Population			
Table 15.2.3.11.1	Descriptive Statistics of Uncorrected Nicotine Plasma PK Parameters following Ad Libitum Use by Sex - PK Population			
Table 15.2.3.12	Analysis of Background-Corrected Nicotine PK Parameters following Ad Libitum Use - PK Population			
Table 15.2.3.12.1	Analysis of Background-Corrected Nicotine PK Parameters following Ad Libitum Use by Sex - PK Population			
Table 15.2.3.12.2	Analysis of Background-Corrected Nicotine PK Parameters following Ad Libitum Use - Sensitivity analysis restricted to P3P 1, 2 and 4 - PK Population			
Table 15.2.3.13	Analysis of Uncorrected Nicotine PK Parameters following Ad Libitum Use - PK Population			
Table 15.2.3.13.1	Analysis of Uncorrected Nicotine PK Parameters following Ad Libitum Use by Sex - PK Population			
Table 15.2.3.13.2	Analysis of Uncorrected Nicotine PK Parameters following Ad Libitum Use - Sensitivity analysis restricted to P3P 1, 2 and 4 - PK Population			
Table 15.2.3.14	Analysis of Background-Corrected and Uncorrected Nicotine ctpeak and tpeak following Ad Libitum Use - PK Population			

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.3.14.1	Analysis of Background-Corrected and Uncorrected Nicotine tpeak and ctpeak following Ad Libitum Use by Sex - PK Population			
Table 15.2.4.1	Descriptive Statistics of VAS Craving Results [mm] and Changes from Baseline following Fixed Puffing Regimen - PK Population	Y		
Table 15.2.4.2	Analysis of VAS Craving Results [mm] following Fixed Puffing Regimen - PK Population			
Table 15.2.4.3	Descriptive Statistics of VAS Craving AUC following Fixed Puffing Regimen - PK Population			
Table 15.2.4.4	Analysis of VAS Craving AUC following Fixed Puffing Regimen - PK Population			
Table 15.2.4.5	Descriptive Statistics of VAS Craving Results and Changes from Baseline following Ad Libitum Use - PK Population	Y		
Table 15.2.4.6	Analysis of VAS Craving Results following Ad Libitum Use - PK Population			
Table 15.2.4.7	Descriptive Statistics of VAS Craving AUC following Ad Libitum Use - PK Population			
Table 15.2.4.8	Analysis of VAS Craving AUC following Ad Libitum Use - PK Population			
Table 15.2.4.9	Descriptive Statistics of mCEQ Questionnaire Subscale Scores - PK Population	Y		
Table 15.2.4.10	Analysis of mCEQ Questionnaire Subscale Scores - PK Population			
Table 15.2.4.11	Descriptive Statistics of Sensory Questionnaire - PK Population			
Table 15.2.4.12	Analysis of Sensory Questionnaire - PK Population			
Table 15.2.4.13	Descriptive Statistics of HPT Parameters Per Puff following Fixed Puffing Regimen - PK Population			

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.4.14	Descriptive Statistics of HPT Parameters Per Product Use following Fixed Puffing Regimen - PK Population	Y		
Table 15.2.4.15	Descriptive Statistics of HPT Parameters Per Puff following Ad Libitum Use - PK Population			
Table 15.2.4.16	Descriptive Statistics of HPT Parameters Per Product Use following Ad Libitum Use - PK Population	Y		
Table 15.2.4.17	Descriptive Statistics of Weight Before and After Use for Fixed Puffing Regimen - PK Population	Y		
Table 15.2.4.18	Descriptive Statistics of Weight Before and After Use for Ad Libitum Use - PK Population	Y		
Table 15.2.6.1	Summary of Adverse Events - Safety Population		Y	
Table 15.2.6.2	Summary of Adverse Events by System Organ Class and Preferred Term - Safety Population		Y	
Table 15.2.6.2.1	Summary of Frequent Adverse Events by System Organ Class and Preferred Term - Safety Population		Y	Y
Table 15.2.6.3	Summary of Adverse Events Related to Study Product by System Organ Class and Preferred Term - Safety Population		Y	
Table 15.2.6.4	Summary of Adverse Events Related to Study Procedures by System Organ Class and Preferred Term - Safety Population		Y	
Table 15.2.6.5	Summary of Expected Adverse Events by System Organ Class and Preferred Term - Safety Population		Y	

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.6.6	Summary of Adverse Events by System Organ Class, Preferred Term and Severity - Safety Population		Y	
Table 15.2.6.7	Summary of Adverse Events by System Organ Class and Preferred Term Leading to Product Discontinuation - Safety Population		Y	
Table 15.2.6.8	Summary of Adverse Events by System Organ Class and Preferred Term Leading to Study Discontinuation - Safety Population		Y	
Table 15.2.6.9	Summary of P3P Product Events and Malfunctions - Safety Population		Y	
Table 15.2.6.10.1	Summary of Clinical Chemistry Parameters - Safety Population		Y	
Table 15.2.6.10.2	Descriptive Statistics of Clinical Chemistry Parameters - Safety Population		Y	
Table 15.2.6.10.3	Shift Tables of Clinical Chemistry Parameters - Safety Population		Y	
Table 15.2.6.11.1	Summary of Hematology Parameters - Safety Population		Y	
Table 15.2.6.11.2	Descriptive Statistics of Hematology Parameters - Safety Population		Y	
Table 15.2.6.11.3	Shift Tables of Hematology Parameters - Safety Population		Y	
Table 15.2.6.12.1	Summary of Urinalysis Parameters - Safety Population		Y	
Table 15.2.6.12.2	Descriptive Statistics of Quantitative Urinalysis Parameters - Safety Population		Y	
Table 15.2.6.12.3	Frequencies of Qualitative Urinalysis Parameters - Safety Population		Y	
Table 15.2.6.12.4	Shift Tables of Quantitative Urinalysis Parameters - Safety Population		Y	

Table 21 Tables, Figures and Listings

Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.6.12.5	Shift Tables of Quantitative Urinalysis Parameters - Safety Population		Y	
Table 15.2.6.13.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 - Safety Population		Y	
Table 15.2.6.13.2	Summary of Prior Medication by Preferred Drug Name - Safety Population		Y	
Table 15.2.6.14.1	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 - Safety Population		Y	
Table 15.2.6.14.2	Summary of Concomitant Medication by Preferred Drug Name - Safety Population		Y	
Table 15.2.6.15	Summary of Physical Examination Findings - Safety Population		Y	
Table 15.2.6.16.1	Interpretation of Vital Signs at Screening, Baseline and Discharge - Safety Population		Y	
Table 15.2.6.16.2	Interpretation of Vital Signs by Product Variant - Safety Population		Y	
Table 15.2.6.16.3	Descriptive Statistics of Vital Signs at Screening, Baseline and Discharge - Safety Population		Y	
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Table 15.2.6.17.1	Interpretation of Spirometry Results - Safety Population		Y	
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Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
Table 15.2.6.19	Summary and Descriptive Statistics of Cough Assessments by Product Variant - Safety Population		Y	
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Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
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Figure 15.1.3.13	Individual Background-Corrected Nicotine Plasma Concentration-Time Profiles following Ad Libitum Use (Linear) - PK Population			
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Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
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Table No.	Title	Topline (Y/N)	Safety (Y/N)	Clinical Trial.gov (Y/N)
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