STATISTICAL ANALYSIS PLAN

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

Sponsor Reference No.: P3P-SE-02-RU

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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 statisticial analysis plan (SAP) has been developed to supplement the statistical analyses described in the clinical study protocol version 2.0 dated 12 June 2019.

This SAP describes the methodology and considerations of the planned analyses and provides a list of all the tables figures and listings (TFLs) for this study. A detailed description of the planned TFLs will be provided in a separate TFL shell 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 research study report (RSR).

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 E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports"
- Electronic case report forms (eCRF) version 4.0 2019 17 Oct .

3.1 Revision History

Version	Date of Revision	Revision
1.0	2019 October 24	Original SAP

4 ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used within this SAP.

ABOUT	Assessment of behavioral outcomes related to tobacco and nicotine products
AE	Adverse event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic and Chemical
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}4h)}$	Partial AUC, assessed between 0 and 4 hours post P3P use
BLOQ	Below the Lower limit of Quantification
BMI	Body mass index
BoExp	Biomarker of exposure
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
C_{max}	Maximum concentration
COT	Cotinine
CRF	Case report form
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events and common toxicity criteria
CTMS	Clinical trial management system
CV	Coefficient of variation
CYP2A6	Cytochrome P450 2A6
DDE	Drug Dictionary Enhanced
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HCOT	Trans-3'hydroxycotine
HIV	Human immunodeficiency virus
HnB	Heat not Burn
HPHCs	Harmful and potentially harmful constituents
ICF	Informed consent form
ICH	International Conference on Harmonization
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
PK	Pharmacokinetic(s)
PMPSA	Philip Morris Products S.A.
PT	Preferred Term
QTcB	QT Interval Corrected using Bazett's Formula

QTcF	QT Interval Corrected using Fridericia's Formula
RSR	Research Study Report
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SOC	System Organ Class
T	Time point
T_0	Time point of start of product use
t_{max}	Time to maximum concentration
TFL	Tables, Figures, and Listings
Total NNAL	Total 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol
ULOQ	Upper limit of quantification
VAS	Visual analogue scale
WBC	White blood cell (count)
WHO	World Health Organization
λ_z	Terminal elimination rate constant

The following special terms are used in this SAP:

Screen failure	Subject who signs the ICF but is not enrolled at Admission.
Enrollment	On Admission Visit (Day -1) for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily assessed and met.
First product use time point	Start of the product test use.
Randomization	Allocation of the respective product, P3P-1mg or P3P-2mg, after product test on Day -1.
End of Study	The end of the study (EOS) for a subject is defined as either the Discharge at Day 30, or the date of early termination of the subject, plus the Safety Follow-Up Period. The end of the whole study corresponds to the individual EOS of the last subject.
Safety Follow-up	After discharge on Day 30 or early termination, a 14-day Safety Follow-Up will be done.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective and Endpoints

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

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

5.2 Secondary Objectives and Endpoints

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

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

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

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

3. To assess nicotine/tobacco product use.

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

4. To assess safety and tolerability during the study.

   Endpoints:
   - Incidence of adverse events (AEs), serious adverse events (SAEs);
   - Frequency of adverse events (AEs), serious adverse events (SAEs);

- Incidence of P3P product events including malfunction/misuse;
- Frequency of P3P product events including malfunction/misuse;
- Physical examination changes from baseline;
- Cough assessment changes from baseline (VAS and three Likert scales);
- Electrocardiogram (ECG) changes from baseline (heart rate, PR, QRS, QT, QTcB, QTcF intervals);
- Vital signs changes from baseline (systolic and diastolic blood pressure, pulse rate and respiratory rate);
- Spirometry changes from baseline (FEV1, FEV1 % predicted, FVC, FVC % predicted, FEF 25, FEF 25 % predicted, FEF 75, FEF75 % predicted, FEF 25-75, FEF 25-75 % predicted, FEV1/FVC);
- Changes from baseline in clinical chemistry, hematology, and urinalysis safety panel;
- Concomitant medications.

5. To assess the exposure to harmful and potentially harmful constituents (HPHCs) in spot urine expressed as concentration adjusted for creatinine from Day -1 to Day 30.

   Endpoints:

   - Biomarker of exposure (BoExp) to nicotine: Nicotine equivalents (NEQ);
   - BoExp to NNK: 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL);
   - BoExp to Acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).

6. To assess tobacco and nicotine containing product dependence at Day -1 and at Day 30.

   Endpoint:

   - ABOUT^{TM}-Dependence Questionnaire.

7. To assess cytochrome P450 2A6 (CYP2A6) enzymatic activity at Day 1 and at Day 30.

   Endpoint:

   - Molar metabolic ratio of trans-3'-hydroxycotinine/cotinine in plasma.

8. To estimate the amount of powder extracted from P3P used for PK assessment.

   Endpoint:

   - Weight difference of P3P before and after use.

5.3 Study Hypotheses And Evaluation Criteria

5.3.1 Hypotheses

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

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a randomized, double-blinded, 2-arm parallel groups, single-center study conducted in current adult smokers willing to switch from smoking cigarettes to using P3P for 1 month. Subjects were asked to use no more than 15 P3P products per day over 1 month and the study will include 2 occasions of confinement period (3 days at V2 and 2 days at V6). From the start of the exposure period onwards, subjects will be instructed to use P3P exclusively. Subjects will be randomized to use either P3P-2mg or P3P-1mg.

1) Screening and Admission (from the ICF Signature [V1] to Randomization at V2 [Day -1]):

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

Subjects will return to the investigational site for Admission (Day -1). Subjects should have been fasting for at least 6 hours prior to Admission. After confirmation of eligibility, subjects will be enrolled. All subjects that are not enrolled will be considered as screen failures. At Admission, enrolled subjects will perform a product test using up to 6 P3P products (alternating between P3P-1mg and P3P-2mg). In order to continue in the study, each subject will need to test at least one product of each P3P variant during the product test. Subjects should be abstinent from the use of any tobacco/nicotine containing products for at least 4 hours prior to product test. After the product test, subjects not willing and/or not ready to use P3P will be discontinued from the study. Subjects willing and ready to use P3P during the study will be randomized either to P3P-1mg or P3P-2mg in a 1:1 ratio and will start their first overnight (confinement) period for pharmacokinetics assessments on Day 1. The subjects and the Investigator will be blinded to the randomization arm.

2) The Exposure Period (from V2 [Day 1] to Discharge at V6 [Day 30]):

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

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

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

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

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

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

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

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

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

After discharge on Day 30 or early termination, subjects will enter a 14-day Safety Follow-Up Period during which new AE/SAEs will be collected and ongoing AEs/SAEs will be

followed-up by the site. At the end of the Safety Follow-Up all subjects will be contacted via phone in order to check the status of the ongoing AEs and also to collect any new AEs experienced by the subjects. Subjects should be contacted 14-days after Day 30. In case they cannot be reached two additional attempts at the next 2 consecutive days will be made. If the subjects cannot be reached after the three attempts they will be declared lost to follow-up. Phone calls should be recorded in the source documents. Any non-serious AE that is ongoing at the time of discharge or early discontinuation or previously reported during the Safety Follow-Up will be followed-up by the Investigator or designee during Safety Follow-Up Period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition) or the subject is lost to follow up. At the end of the Safety Follow-Up Period, all ongoing non-serious AEs will be documented as "ongoing" and no further follow-up information will be sought for them by the Investigator or designee. At that point, the Investigator will assess whether the subject should be referred to his/her General Practitioner to have their ongoing AEs addressed accordingly. All SAEs will be followed up by the Investigator until resolution, stabilization or the determination of a plausible explanation for them was found, regardless of the end of the Safety Follow-Up Period.

6.2 Selection of Study Population

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

6.2.1 Inclusion Criteria

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

Inclusion Criteria	Rationale	Screening	Admission (Day -1)
1. Subject has signed and dated the ICF and is able to understand the information provided in it.	Administrative	X	
2. Subject is male or female aged between 21 and 65 years old inclusive.	Safety	X	
3. Subject has been a smoker for at least the last 3 years prior to the Screening visit and has smoked 5 to 15 commercially available cigarettes per day over the last 3 months prior to Screening.	Effect	X	
4. Subject has a positive urinary cotinine test (cotinine ≥ 200 ng/mL).	Effect	X	X

5. Subject does not plan to quit smoking in the next 2 months.	Safety	X	X
6. Smoking, healthy subject as judged by the Investigator or designee based on available assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, chest X-ray, ECG and medical history).	Safety	X	
7. Availability for the entire study period and willingness to comply with study procedures, including intermittent dietary restrictions.	Effect	X	X
8. Ready to switch from smoking cigarettes to using P3P for the duration of the study.	Effect	X	

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

Exclusion Criteria	Rationale	Screening	Admission (Day -1)
4. As per the Investigator's judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.	Effect	X	
5. Subject has asthma condition (post-bronchodilator $FEV_1/FVC < 0.75$ and reversibility in $FEV_1 \geq 12\%$ and > 200 mL from pre- to post-bronchodilator values).	Safety	X	
6. Subject has $(FEV_1/FVC) < 0.7$ and $FEV_1 < 80\%$ predicted value at post-bronchodilator spirometry.	Safety	X	
7. Subject has a history of hypersensitivity to [redacted] or menthol.	Safety	X	
8. Subject has a contraindication for using salbutamol and/or albuterol as per the summary of product characteristics for the given product	Safety	X	
9. Subject has donated or received whole blood or blood products within 3 months prior to Screening Visit.	Safety	X	
10. BMI < 18.5 kg/m^2 or ≥ 32.0 kg/m^2.	Safety	X	
11. Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer) which has an impact on CYP2A6 activity.	Effect		X
12. Subject has a positive serology test for HIV 1/2, Hepatitis B, or Hepatitis C.	Safety	X	
13. The subject has a positive alcohol breath test and/or had a history of alcohol disorder within the past 2 years.	Administrative	X	X
14. The subject has a positive urine drug test.	Administrative	X	X
15. Subject or one of their family members[a] is a current or former employee of the tobacco industry.	Administrative	X	

Exclusion Criteria	Rationale	Screening	Admission (Day -1)
16. Subject or one of their family members[a] is employee of the investigational site or of any other parties involved in the study.	Administrative	X	
17. The Subject has participated in another clinical study within 3 months prior to the Screening Visit.	Safety	X	
18. Subject has been previously screened or enrolled in this study.	Administrative	X	
19. Subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding.	Safety	X	X
20. For women of childbearing potential only[b]: subject does not agree to use an acceptable method of effective contraception.[c]	Safety	X	

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

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

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

6.3 Product Allocation and Blinding

6.3.1 Methods of Assigning Subjects to Product Variant

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

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

6.3.2 Blinding

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

7 DERIVED AND COMPUTED VARIABLES

Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint.

Baseline definition by endpoint can be found in the different sections defining the derivation of each endpoint below and in section 12.1.4.

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

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

where var = the variance from the log transformed data.

7.1 Pharmacokinetic Parameters

For the calculation of PK parameters, the actual blood sampling times (collected in the CRF) rather than the nominal timepoints will be used in all calculations with the exception of the last collected sample prior to product use which can be considered as the T_0 value. Partial dates/times for PK assessments or T_0 will not in general be imputed.

For nicotine concentrations below the lower limit of quantification (BLOQ) :

- BLOQ values before T_0 will be imputed by LLOQ/2.
- BLOQ values after the last quantifiable value are not included in the analysis (e.g., for the calculation of AUC).
- Any BLOQ value (after T_0 and before the last quantifiable value) would need to be queried and, if confirmed, it will be imputed by LLOQ/2.

To minimize the carry-over effect in the plasma nicotine PK parameters due to limited washout periods, background-concentration correction will be applied to the nicotine concentration data.

Baseline nicotine concentration (C_0) will be defined as the last measured concentration prior to T_0 at Day 1 and at Day 30 (Visit 2 and Visit 6). The baseline correction will be implemented by calculating the PK parameters using adjusted concentration values as described below:

- Calculate the slope using a linear regression on the log concentration of the 3 pre-T_0 timepoints.
- If the slope is ≤ 0, then use the slope to determine the elimination rate constant λ_z.

- If the slope is > 0, then use the subject's slope that is ≤ 0 from the other visit to determine λ_z. If the subject's slopes are positive for the 2 visits, baseline corrected PK parameters will not be calculated.
- Adjust each concentration value post-baseline using the following formula:

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

cCt is the corrected concentration at each time point, Ct is the concentration at each time point, C_0 is the pre-use baseline nicotine concentration at the given visit, λ_z is the elimination rate constant and t is the actual time.

If C_0 is BLOQ then there will be no baseline correction of the PK parameters. In that case cC_{max}, ct_{max} and $cAUC_{(0-4h)}$ will be considered as equal to C_{max}, t_{max} and $AUC_{(0-4h)}$, respectively.

- The following PK parameters will be derived from nicotine levels adjusted for baseline:

cC_{max}	Background-corrected maximum observed plasma concentration. cC_{max} will be reported as long as there is at least one quantifiable concentration post-exposure
ct_{max}	Time to maximum concentration cC_{max}
$cAUC_{(0-4h)}$	Background-corrected area under the plasma concentration-time curve from start of product use (T_0) to 4 hour

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

7.1.1 Calculation of C_{max} , cC_{max} , t_{max} , and ct_{max}

The minimum requirement for the determination of the C_{max} and the cC_{max} is the inclusion of at least one quantifiable concentration within 1 hour post-exposure.

If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of the C_{max}, similarly for cC_{max}.

7.1.2 Calculation of AUC

The minimum requirement for the calculation of the AUC is the inclusion of at least 3 plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

$AUC_{(0-4h)}$ will be calculated using the linear trapezoidal method with the first value being C_0 and the last value being the last measurement performed at the 4h post T_0 timepoint.

If the 4h post T_0 timepoint is missing, the $AUC_{(0-4h)}$ will be set to missing.
If the 4h post T_0 timepoint is collected between 3h and 3h30min post T_0, the 4h post T_0 concentration will be extrapolated using the slope of all timepoints after t_{max}.
If the 4h post T_0 timepoint is collected after 4h30 post T_0, the 4h post T_0 concentration will be interpolated using the slope of all timepoints after t_{max}.

Similar rule will be applied for the calculation of $cAUC_{(0-4h)}$.

7.1.3 Anomalous Values

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 will be reviewed for inclusion in the analysis during the pre-analysis data review.

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, interruption 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.

7.2 Pharmacodynamic effects

7.2.1 Visual Analogue Scale for Craving

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

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

For Day 1 and Day 30, baseline VAS-craving is defined as the measurement obtained at 10 ± 2 min prior to the T_0 at Day 1 and Day 30, respectively.

Baseline for this endpoint is therefore different at Day 1 and Day 30.

VAS craving score and changes from baseline will be summarized by timepoint within Day 1 and Day 30. In addition, at Day 1 and Day 30, $AUC_{VAS(0-4)}$ will be derived using the linear trapezoidal method. For the calculations of $AUC_{VAS(0-4)}$, the actual timepoints of VAS

assessements instead of nominal timepoint will be used. The first VAS value to be taken into account in the derivation of $AUC_{(0-4)}$ is the value obtained 10 min prior to the T_0 timepoint, which will be considered as value at T_0.The last value being the last measurement performed at the 4h post T_0 timepoint.

If the 4h post T_0 timepoint is missing, the $AUC_{VAS(0-4)}$ will be set to missing.

If the 4h post T_0 timepoint is collected after 3h but prior to 3h50 post T_0, the 4h post T_0 the score will be derived using the extrapolation at 4h based on the last 2 timepoints collected prior to 4h.

If the 4h post T_0 timepoint is collected after 4h10 but prior to 5h post T_0, the 4h post T_0 score will be interpolated between the last 2 timepoints.

7.2.2 Sensory Questionnaire

A sensory questionnaire will be completed by each subject at Day 1 and Day 30 within 60 minutes after the P3P product use for PK assessment. The sensory questionnaire assesses the subject's opinion on the following sensory parameters:

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

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

Each item will be analysed individually, no total score will be computed.

Table 1: Sensory Questionnaire - Questions

Question	
1	How much did you like the puff 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?

Reported values at Day 1 will be considered as baseline values.

7.2.3 ABOUT™-Product Experience

Product Experience will be assessed via a subject self-reported outcome measure at Day 1 and Day 30 within 60 minutes after the P3P product use for PK assessment, using the ABOUT™-Product Experience Questionnaire.

The questionnaire consists of three multi-item scales and two single-item scales.

The questionnaire assesses the degree to which subjects experience the reinforcing effects of P3P use by measuring:

- Product satisfaction (satisfying, tastes good, enjoy the product – Questions 1, 2, and 12).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger – Questions 4 to 8).
- Aversion (dizziness, nausea – Questions 9 and 10).
- Enjoyment of respiratory tract sensations (single-item assessment – Question 3).
- Craving reduction (single-item assessment – Question 11).

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

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

Reported values at Day 1 will be considered as baseline values.

7.3 Product acceptance and puffing/inhalation behavior

7.3.1 Product Acceptance Questionnaire

At Day 1 and Day 30, subjects will complete the product Acceptance Questionnaire. This questionnaire will be used to assess product characteristics of P3P relevant to determine subjects’ acceptability of the product. Subjects will be asked to rate P3P in terms of sensory attributes, ease of use and occasions of use.

A baseline version of the product acceptance questionnaire consisting of 5 questions will be answered at Day 1, while a 6-questions version containing an additional question asking about occasions of P3P use will be answered at Day 30.

Answers to questions 1 to 4 will be considered continuous while anwers to questions 5 and 6 will be presented using frequencies.

Reported values at Day 1 will be considered as baseline values.

Table 2: Product Acceptance - Questions

Question	Answer
1. What is your overall opinion about P3P	I dont like it at all =1, 2, 3, 4, 5, 6 to 7 = I like it very much
2. a. What is your opinion on P3P's taste intensity?	Not intense at all =1, 2, 3, 4, 5, 6 to 7 = Very intense
2. b. What is your opinion on P3P's aftertaste intensity?	Same as above
2. c. What is your opinion on P3P's cooling intensity?	Same as above
2. d. What is your opinion on P3P's visibility of exhale?	I dont like it at all =1, 2, 3, 4, 5, 6 to 7 = I like it very much
2. e. What is your opinion on P3P's acoustic feedback(sound)?	Same as above
2. f. What is your opinion on P3P's tactile feedback (vibration)?	Same as above
2. g. What is your opinion on P3P's having no electronics/needing no charging?	Same as above
2. h. What is your opinion on P3P's length of expirience?	Same as above
2. i. What is your opinion on P3P's consistency of sensation beetwen puffs?	Same as above
3. a. Please indicate how easy you consider piercing the capsule to be?	Not intense at all =1, 2, 3, 4, 5, 6 to 7 = Very intense
3. b. Please indicate how easy you consider understanding when P3P is activated to be?	Not easy at all =1, 2, 3, 4, 5, 6 to 7 =Very easy
3. c. Please indicate how easy you consider drawing on P3P to be?	Same as above
3. d. Please indicate how easy you consider inhaling to be?	Same as above
3. e. Please indicate how easy you consider understanding the end of P3P use to be?	Same as above
4. a. What is your opinion on P3P when you compare it to pipe?	I like P3P much less = 1, 2, 3, 4, 5, 6 to 7 = I like P3P much better (I did not use this = missing)
4. b. What is your opinion on P3P when you compare it to Hookah?	Same as above
4. c. What is your opinion on P3P when you compare it to Heat-not-burn tobacco?	Same as above
4. d. What is your opinion on P3P when you compare it to e-cigarette?	Same as above
4. e. What is your opinion on P3P when you compare it Snuff or chewing tobacco?	Same as above
4. f. What is your opinion on P3P when you compare it to Nicotine Replacement Therapy (e.g. patches, gum) ?	Same as above
5. After consuming one P3P, which statement best describes how you feel?	I feel satisfied

	I do not feel satisfied and want to use another P3P again shortly afterwards I do not feel satisfied and want to consume one of my regular cigarettes shortly afterwards
6. What are three occasions on which you were using P3P the most during the last month?	At home, indoors At home, outdoors (e.g. garden, balcony) In areas where I don't normally smoke (e.g. at my desk at place of work) In a designated outdoor smoking area at my place of work In a designated indoor smoking area at my place of work In a designated indoor or outdoor smoking area (e.g. terrace) in a bar, restaurant, cafe or nightclub In public areas (e.g. in the street, in a park) At a friend or colleague's home At a family member's home In the car

7.3.2 Puffing/ Inhalation behavior question

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

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

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

Reported values at Day 1 will be considered as baseline values for the site staff assessment while reported values at Day 2 will be considered as baseline values for the subject assessment.

7.3.3 Nicotine/tobacco product use

Subjects will enter the number of P3P consumables used per day, the number of cigarettes used per day, or/and other tobacco and nicotine containing products used per day in a product use diary from Day 1 until the Discharge at V6 (including during the visits). For subjects who decide to quit using all tobacco and nicotine containing products the product use will no longer be captured. See section 7.9 for the definition of product exposure periods.

Average P3P consumables used per day during a period = Total number of P3P consumables used during the period/ duration of the period.

Similar definition will be made for:

- Average Cigarettes smoked per day during a period
- Average Heat not burn and/or smokeless tobacco products used per day during a period
- Average Other tobacco products (pipe, cigar, cigarillos, chewable…) used per day during a period
- Average occasions Electronic Cigarette used per day during a period

Also, the percentage of subjects having used any Nicotine Replacement Therapies over the period will be provided.

Change from baseline in average number of cigarettes used per day = Average number of cigarettes used per day reported at Screening - Average number of cigarettes used per day per period.

7.4 Nicotine Equivalents, CEMA, and Total NNAL

7.4.1 Values outside limits of quantification

Values below the lower limit of quantification (BLOQ) will be imputed using 0.5 x lower limit of quantification. For values above the upper limit of quantification (ULOQ), i.e., preceded by a ">", for example ">xx," the numerical xx will be used for calculation and reporting in summary tables.

7.4.2 Nicotine Equivalents in Urine

- Nicotine equivalents (NEQ = molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-glucuronide) will be adjusted for creatinine in spot urine.

$$\begin{aligned} \text{NEQ [mg]} = {} & (\text{free nicotine}_c\ [\mu\text{mol/L}] + \text{nicotine-glucuronide}_c\ [\mu\text{mol/L}] \\ & + \text{free cotinine}_c\ [\mu\text{mol/L}] + \text{cotinine-glucuronide}_c\ [\mu\text{mol/L}] \\ & + \text{free } \textit{trans}\text{-3'-hydroxycotinine}_c\ [\mu\text{mol/L}] \\ & + \textit{trans}\text{-3'-ydroxycotinine-glucuronide}_c\ [\mu\text{mol/L}]) \\ & *162.2\ [\mu\text{g/}\mu\text{mol}]*\text{urine volume [L]} / 1000\ [\mu\text{g/mg}] \end{aligned}$$

N.B. All concentrations must be in µmol/L before applying the above formula.

The conversion factors will be applied as follows:

Free nicotine	The molecular weight is 162.232 g/mol. Therefore to convert nicotine from ng/mL to nmol/L, the result in ng/mL is multiplied by 6.164.
Nicotine glucuronide	The molecular weight is 338.356 g/mol. Therefore to convert nicotine from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.955.
Cotinine	The molecular weight is 176.218 g/mol. Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL will be multiplied by 5.675.
Cotinine-glucuronide	The molecular weight is 352.341 g/mol. Therefore to transform cotinine from ng/mL to nmol/L, the result in ng/mL will be multiplied by 2.838.
Trans-3'hydroxycotinine	The molecular weight is 192.217 g/mol. Therefore to transform trans-3' hydroxycotinine from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.202.
Trans-3'hydroxycotinine-glucuronide	The molecular weight is 368.34 g/mol. Therefore to transform trans-3' hydroxycotinine from ng/mL to nmol/L, the result in ng/mL is multiplied by 2.715.

7.4.3 Concentrations adjusted for creatinine

Concentrations adjusted for creatinine in spot urine collection will be calculated as:

$$\text{Biomarker (adjusted for creatinine)} = \frac{[\text{Biomarker}]}{[\text{Creatinine}]}$$

where the [ ] indicated concentrations measured from the same spot urine collection.

This applies to NEQ, CEMA and total NNAL.

7.5 Tobacco and nicotine containing product dependence

7.5.1 ABOUT™ Dependence Questionnaire

Perceived dependence on tobacco and nicotine-containing products will be assessed via a subject self-reported outcome measure at V2 (Day -1), and at V6 using the ABOUT™-Dependence Questionnaire.

The value recorded at Day -1 will be considered the baseline value.

The questions or items to be answered by the subject in the ABOUT ™ – Dependence Questionnaire are listed in Table 3.

Subjects will be asked to respond to the items in the questionnaire on a Likert type scale. For items 3a-3d, the response to and scoring of items are: 0 = "Not at all"; 1 = "A little"; 2 = "Moderately"; 3 = "Very much"; 4 = "Extremely". For items 4a to 4j, the scoring of items are: 0 = "Never"; 1 = "Rarely"; 2 = "Sometimes"; 3 = "Most of the time"; 4= "All the time".

For the purpose of deriving a score from ABOUT™-Dependence questionnaire for an individual, 3 multi-items domains will be considered: the behavioral impact domain (items 3a, 3b, 4a, 4c, 4e), the signs and symptoms domain (items 4b, 4d, 4f, 4g, 4h) and the extent of use domain (items 1 and 2). The raw score for each domain will be derived by adding the score of each indidual items within the domain and a composite raw score obtained by adding the score of each of the 3 domains.
An overall maximum composite raw score of 50 can be derived from the instrument as follows: 10 from the 'extent of use' domain (the 6-point Likert-type scale produces a maximum raw score of 5 for each item ['0' more than 3 hours to '5' 0 to 5 minutes]), and 20 for each of the other two domains (the 5-point Likert-type scale produces a maximum raw score of 4 for each item, ['0' not at all/never to '4' extremely/all the time]).

The conversion tables below will then be used to derive the corresponding measure score which represents, for that individual, the level of perceived dependence associated with their tobacco and nicotine product (TNP) use. Table 4 provides the conversion for each domain for the transformation of participant raw score to the measure score ranging from 0 to 100 as measured separately by each of the extent of use, behavioral impact, and signs and symptoms domain.

Table 5 provides the conversion for the composite score from all three domains for the transformation of total raw score to the measure score ranging from 0 (no perceived dependence) to 100 (very high perceived dependence) as measured overall with the ABOUT™-Dependence questionnaire. There are also separate columns in the conversion table for the composite score based on TNP use types (e.g., multiple users of two or more TNPs), and different categories of exclusive TNP users. This takes into account the adjustment for differential item functioning by TNP user types and different categories of TNPs for the extent of use domain items in relation to the other two domains when computing the three domain composite raw score and measure score.

Note that scores cannot be accurately computed if there are missing responses for any item and no imputation of missing responses will be performed. (See Assessment of Behavioral Outcomes related to Tobacco and nicotine products. – Dependence - User Manual. First Edition. June 2019. PMPSA)

Table 3: ABOUT™ - Dependence – Domains and Questions

Domain	Question	Range for Score
Extent of Use	1.Over the past 7 days, on average, how soon after you woke up did you use your first product?	0 to 5
	2. Over the past 7 days, on average, how long before going to sleep did you use your last product?	0 to 5
Signs and Symptoms	3.a. Currently how much do you feel you need your product(s) to function "normally"?	0 to 4
	3.b. Currently how difficult do you think it would be for you to cut down on your product(s)?	0 to 4
	4.a. Over the past 7 days, how often did you have a strong desire to use your product(s)?	0 to 4
	4.c. Over the past 7 days, how often did you feel that you "HAD to have one"?	0 to 4
	4.e. Over the past 7 days, how often did you use an excuse so you could use your product(s)?	0 to 4
Behavioral Impact	4.b. Over the past 7 days, how often did you use more of your product(s) than you intended to?	0 to 4
	4.d. Over the past 7 days, how often did you use your product(s) in a situation where you weren't supposed to?	0 to 4
	4.g. Over the past 7 days, how often did you sneak off to use your product(s)?	0 to 4
	4.h. Over the past 7 days, how often did you avoid an activity because you could not use your product(s)?	0 to 4
Individual Questions not to be grouped	3.c. Currently how addicted to the product(s) do you consider yourself?	0 to 4
	3.d. Currently how difficult do you think it would be for you to completely quit your product(s)?	0 to 4
	4.i. Over the past 7 days, how often did you stop what you were doing to use your product(s)?	0 to 4
	4.j. Over the past 7 days, how often did you find youself using your product(s) automatically (without thinking about it)?	0 to 4

Table 4: ABOUT™ - Dependence sum score to measure conversion By Domain

Extent of Use Domain	Total raw score (complete data)	Measure score (transformed 0-to-100 scale)
	0	0
	1	17
	2	28
	3	36
	4	43
	5	50
	6	57
	7	64
	8	73
	9	85
	10	100
Behavioral Impact Domain	**Total raw score (complete data)**	**Measure score (transformed 0-to-100 scale)**
	0	0
	1	14
	2	23
	3	29
	4	34
	5	38
	6	41
	7	44
	8	47
	9	50
	10	53
	11	56
	12	59
	13	62
	14	65
	15	69
	16	73
	17	77
	18	82
	19	90
	20	100
Signs and Symptoms Domain	**Total raw score (complete data)**	**Measure score (transformed 0-to-100 scale)**
	0	0
	1	11
	2	19
	3	25
	4	30
	5	34
	6	37
	7	41
	8	44
	9	48
	10	51
	11	55
	12	58

13	62
14	66
15	70
16	74
17	79
18	84
19	91
20	100

Table 5: ABOUT - Dependence sum score to measure conversion for the questionnaire composite score

	Users of two or more TNPs	Exclusive users: P3P, HnB, Cigarettes, Smokeless tobacco, Pipe, NRTs	Exclusive users: e-Cigarettes	Exclusive users: Waterpipe, Cigars
Composite raw score (complete data)	**Measure score (transformed 0-to-100 scale)**	**Measure score (transformed 0-to-100 scale)**	**Measure score (transformed 0-to-100 scale)**	**Measure score (transformed 0-to-100 scale)**
0	0	0	0	0
1	15	16	13	16
2	22	22	20	23
3	26	27	25	28
4	30	30	29	31
5	32	32	31	34
6	35	35	34	36
7	37	36	36	38
8	38	38	38	40
9	40	40	39	42
10	42	41	41	43
11	43	43	42	45
12	44	44	44	46
13	46	45	45	47
14	47	47	46	48
15	48	48	47	49
16	49	49	48	50
17	50	50	49	51
18	51	51	50	52
19	52	52	51	53
20	53	53	52	54
21	54	54	53	54
22	55	55	54	55
23	56	55	54	56
24	57	56	55	57
25	58	57	56	57
26	58	58	57	58
27	59	59	58	59
28	60	59	58	59
29	60	60	59	60
30	61	61	60	61
31	62	61	61	61
32	62	62	61	62
33	63	63	62	63
34	64	63	63	63
35	64	64	63	64
36	65	65	64	65
37	66	65	65	65
38	66	66	65	66
39	67	67	66	67
40	68	68	67	67
41	69	68	68	68
42	70	69	69	69

43	71	70	69	70
44	72	71	71	71
45	73	73	72	73
46	75	75	73	74
47	77	77	75	77
48	81	80	78	80
49	87	86	83	87
50	100	100	100	100

The category of exclusive users at Day -1 are defined based on the tobacco and nicotine containing products use history/habits questionnaire:

- A subject will be a cigarette user if their average cigarette consumption over the last 3 months is greater or equal to 1 per day.
- A subject will be Pipe, or Smokeless tobacco, or NRTs user at Day -1 if Yes is answered to use of pipe, OR snuff or chewing tobacco OR NRT respectively among the tobacco/nicotine containing products listed in question 6 of the tobacco and nicotine containing products use history/habits for last 7 days
- A subject will be e-cigarette user at Day -1 if Yes is answered to use of e-cigarette among the tobacco/nicotine containing products listed in question 6 of the tobacco and nicotine containing products use history/habitsfor last 7 days
- A subject will be users of waterpipe at Day -1 if Yes is answered to use of Hookah among the tobacco/nicotine containing products listed in question 6 of the tobacco and nicotine containing products use history/habitsfor last 7 days

Exclusive user if Y in any category and N to others.

Exclusive users at end of study

At the end of the study, the flag will be based on **ALL** the e-diary data prior to Day 30:

- Subject will be Cigarettes or Smokeless tobacco or Pipe, or NRTs user at Day 30 if average use of any of the above ≥1/day
- Subject will be e-cigarette user at Day 30 if average use of e-cigarette ≥1 per day
- Subject will be user of waterpipe or cigars at Day 30 if average use of pipe, cigars, or cigarillos ≥1 per day

7.6 CYP2A6

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

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

Any values below the LLOQ or above the upper limit of quantification (ULOQ) in the component parameters will not be imputed and the derived variable will be set to missing.

The conversion factor will be applied as follows:

Cotinine (COT)	The molecular weight is 176.2178 g/mol. 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. Therefore to transform HCOT from ng/mL to nmol/L, the result in ng/mL is multiplied by 5.202.

The converted results will be reported to three decimal places and the ratio will be reported as a percentage.

Value obtained at Day 1 prior to any product use will be considered the baseline value.

7.7 Weighing of P3P Products

At Day 1 and Day 30, P3P used for PK assessment should be weighed before product use and as early as possible (but within maximum 1 hour) after the end of product use. Weight difference (before – after product use) will be calculated.

7.8 Safety Variables

7.8.1 ECG

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

$$QTcF = \frac{QT}{\sqrt[3]{(60/HR)}}$$

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

$$QTcB = \frac{QT}{\sqrt[2]{\left(60/HR\right)}}$$

7.8.2 Cough Assessment

At V2-V6, subjects will be asked if they have experienced a regular need to cough, e.g., whether they have coughed several times in the previous 24 hours prior to assessment. If the answer is 'yes', they will be asked to complete a cough assessment questionnaire (which includes a VAS and three Likert scales).

The VAS will assess how bothersome cough is to the subject, on a 10 cm scale ranging from 'not bothering me at all' to 'extremely bothersome'.

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 6: Cough Assessment Likert Scales.

Table 6: Cough Assessment Likert Scales

	Question	Likert Scale
1	The intensity of cough	1 = very mild 2 = mild 3 = moderate 4 = severe 5 = very severe
2	The frequency of cough	1 = rarely 2 = sometimes 3 = fairly often 4 = often 5 = almost always
3	The amount of sputum production	0 = no sputum 1 = a moderate amount of sputum; 2 = a larger amount of sputum; 3 = a very large amount of sputum.

7.9 Categorical Variables

The categorical variables used in this study are shown below (Table 7).

Table 7:Categorical Variables Definitions Other Than Reported in eCRF

Variable	Categories	
Demographics		
BMI (kg/m^2)	Underweight:	< 18.5
	Normal range:	≥ 18.5 and < 25.0
	Overweight:	≥ 25.0 and < 30.0
	Obese:	≥ 30.0
Product Exposure Categories	≤5 P3P-1mg /Day >5-10 P3P-1mg /Day >10 P3P-1mg /Day ≤5 P3P-2mg /Day >5-10 P3P-2mg /Day >10 P3P-2mg /Day	
Product Exposure Periods		
Detailed Product Exposure Periods	Product test Day 1 Day 2 Period 1 ([D3 –V3]) Period 2 ((V3-V4]) Period 3 ((V4-V5]) Period 4 ((V5-V6])	
Overall exposure period	Day 1 to Day 29 inclusive	

7.10 Timepoints

Endpoints collected at the various visits and Day within visit will be labelled according to the Table below.

There will be a one-to-one association between the visit number and the timepoint used in the analysis.

Table 8: Timepoints Description

Timepoint	Label in Table
V1	Screening
V2 - Admission	Product Test
V2 – Day 1	Day 1
V2 – Day 2	Day 2
V3	Day 7
V4	Day 15
V5	Day 22

Table 8: Timepoints Description

Timepoint	Label in Table
V6 – Day 29	Day 29
V6 – Day 30	Day 30

8 SAMPLE SIZE JUSTIFICATION

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

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

The following changes with respect to the analysis populations were made in the SAP compared to the Protocol:

- Changes regarding Population of Subjects to be Used for Different Endpoints

Endpoints	Protocol	SAP
Pharmacodynamics (VAS craving, Sensory questionnaire, ABOUT™ -Product Experience)	PK	Randomized
Product Acceptance	PK	Randomized
Puffing Inhalation Behavior	PK	Randomized

In addition, results for the 2 variants combined will not be reported except for data collected at baseline.

- Changes regarding Analysis Model for PK and AUC for VAS craving score

In the protocol, an ANOVA model with sex and product exposure category as factors was anticipated to be used to compare PK parameters and AUC for VAS craving score between variants at Day 30. The ANOVA model was replaced by an ANCOVA model with sex and product exposure category as factors and Day 1 value as covariate.

No Day 1 comparisons will be performed. Within-group comparisons Day 30 versus Day 1 will also be performed in an ANOVA model with sex and product exposure category as factors.

10 ANALYSIS POPULATIONS

10.1 Screened Population

The screened population consists of all the subjects who give informed consent.

10.2 Safety Population

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

10.3 Randomized Population

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

10.4 PK Population

The PK population is a subset of the randomized population and consists of all subjects who completed at least one of the single use of P3P for PK assessment, and for whom at least one primary nicotine PK parameter can be derived. Only subjects without major protocol deviations that impact evaluability of the data (see Section 11 “Protocol Deviations”) will be included in the PK analysis sets.

11 PROTOCOL DEVIATIONS

Protocol deviations are defined as deviations from the study procedures, including but not limited to any violation of inclusion/exclusion criteria, assessments not performed or performed outside the scheduled time windows, or use of drugs that are known to affect study endpoints.

All protocol deviations will be entered into the clinical trial management system (CTMS) or other approved format.

All deviations will be reviewed and 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 subject for the primary objectives of the study and therefore should result in the subject being excluded from the primary analysis population.

11.1 Major Protocol Deviations

Subjects with major protocol deviations will be identified (at a population level) to determine whether they will be excluded from any of the analysis populations. The following have been identified as the major protocol deviations.

The categories for the major deviations will include, but are not limited to the deviations presented in Table 9.

Table 9: Definition of Major Protocol Deviations

Category	Description
Violation	Violation of inclusion/exclusion criteria (see below table)
Mis-randomization	Being administered the wrong product according to the randomization schedule during the entire exposure period
Mis-use of product (PK)	• Use of any nicotine or tobacco–containing product during the wash-out periods. • Inadequate use of P3P product for PK assessment on D1 or D30 (eg. Product not used at all, product not pierced,…)
Concomitant medication	Medications within 5 half-lives of the drug prior to D1 or D30 with an impact on CYP2A6 activity
Visit missing	Subject did not attend a scheduled visit
GCP Deviation	Samples being analyzed in spite of written withdrawal of consent for analysis
Reporting of product use	Less than 75% of the daily product use reported in the e-diary over a period is available, or daily product use not reported over a period of more than 7 consecutive days

Violation of exclusion criteria 11 (Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer) which has an impact on CYP2A6 activity) will be considered as preventing the evaluation of the primary objective. Such deviations will be considered as major and rendering the subject data non-evaluable for the primary objective.

Among the eligibility criteria, violations of inclusion criteria 2, 3 and 4, or of the exclusion criteria 10 will be assessed for their impact on the evaluability of the primary objectives during the pre-analysis data review meeting.

11.2 Minor Protocol Deviations

The categories for the minor deviations will include, but are not limited to the deviations presented in Table 10.

Table 10: Definition of Protocol Deviation Categories

Category	Description
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 11: Definition of Assessment Windows).
Time deviation (other assessments)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Table 11: Definition of Assessment Windows)
Assessment missing (Plasma nicotine PK sample)	PK Assessment is missing
Assessment missing (other assessment)	Assessment is missing
Procedural violation	Violation of planned procedure
Mis-use of product (other)	Use of the wrong P3P variant for a limited period; use of more than 15 P3P products on a single day

11.2.1 Assessment Windows

On Day 1 (V2) and Day 30 (V6), after at least 10 hour abstinence from any tobacco/nicotine containing products, subjects will use a single P3P product, as randomized, for a duration of up to 15 minutes. The start of product use (first puff taken) will be defined as T_0.

The windows reported in Table 11: Definition of Assessment Windows will be applied to the timing of data collection.

Table 11: Definition of Assessment Windows

Assessment	Nominal Time point(s) (relative to T_0)	Window
Plasma nicotine PK sample	**Baseline**	
	1hr , 30 min prior T_0	± 5 minutes
	5 min	± 2 minutes
	Post Baseline (post T_0)	
	4, 7, and 10 min	± 1 min
	15, and 30 min	± 2 min
	1, 2, and 4h	± 5 min
VAS	**Baseline**	
	10 min prior T_0	± 2 minutes
	Post Baseline (post T_0)	
	4, 10, and 15 min	± 2 min
	30 min	± 5 min
	1, 2, and 4h	± 10 min

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

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Data analysis will be performed using SAS® Version 9.3 or higher.

Data listings will be provided for all data collected, ordered by P3P variant and subject, unless otherwise stated. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. All unscheduled assessments will be included in the listings only.

12.1.1 Stratified Presentation

Data summaries will be produced by P3P variant and time point (if applicable), unless otherwise stated.

Stratified presentations by sex and product exposure category will be conducted on the randomized population for the following endpoints:

- Demographics and baseline characteristics
- VAS craving, Sensory questionnaire, and ABOUT™-Product Experience questionnaire
- Product acceptance questionnaire
- Biomarkers to HPHCs (NEQ, CEMA, and total NNAL)
- Puffing/inhalation behavior (only by product exposure category)
- ABOUT™-Dependence questionnaire (only by product exposure)
- CYP2A6

Stratified presentations by actual product exposure category will be conducted on the PK population for the following endpoints:

- Demographics and baseline characteristics
- PK parameters
- Weight difference of P3P

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

- PK parameters

Stratified presentations by actual product exposure category will be conducted on the Safety population for the following endpoints:

- Demographics and baseline characteristics
- Cough assessment
- ECG
- Vital Signs
- Spirometry

12.1.2 Subgroup Analyses

No subgroup analyses are planned.

12.1.3 Descriptive Statistics

All data will be presented in listings.

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

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

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

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

Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Summaries on Safety population will be produced by randomization group and overall, including the available data from subjects who tested the product but were not randomized.

The following product labels and descriptions will be used for the TFLs (Table 12):

Table 12: Product Labels

Randomization Group/P3P Variant	Format used in TFLs	Order in TFLs
P3P-1mg	P3P-1mg	1

P3P-2mg	P3P-2mg	2

The following stratification labels (Table 13) for the TFLs will be used:

Table 13: Stratification Labels

Stratification Factor	
Sex	Male Female
Product Exposure Category	≤5 P3P/Day >5-10 P3P/Day >10 P3P/Day

12.1.4 Definitions of Baseline for Statistical Data Analysis

Baseline values for pharmacodynamic parameters (VAS Craving, Sensory Questionnaire, ABOUT™-Product experience), Product Acceptance, ABOUT™-Dependence, and Puffing/Inhalation behavior questions are defined in section 7.1, 7.2.1, 7.2.2, 7.2.3, 7.3.1, 7.5.1 and 7.3.2 respectively.

Baseline values of BoExp will be defined as the value measured on V2 (Day -1) when spot urine should be collected prior to product test. Baseline for CYP2A6 will be defined as the value determined on Day 1, see section 7.6.

For safety parameters the last assessment prior to product test at Day -1 will be considered as baseline.

12.1.5 Handling of Unplanned Data

Unscheduled post-product use assessments will be excluded from the summary statistics. 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.

12.1.6 Multiple Comparisons / Multiplicity

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

12.1.7 Definitions of Product Exposure Categories

Product exposure categories will be created by calculating the average P3P consumption over the exposure period (from Day 1 to Day 29) as the total number of P3P consumables used during the exposure period / duration of the exposure period.

Subjects will be categorized according to their average P3P consumption in one of the 3 product exposure categories by variant (total of 6 subgroups):

- ≤5 P3P/Day

- >5-10 P3P/Day
- >10 P3P/Day

12.2 Disposition of Subjects

The number and percent of subjects will be summarized for the following categories: subjects screened, screening failed, enrolled subjects, enrolled and not randomized, randomized subjects, completed, and discontinued.

Reasons for screen failure will be summarized in the screened population.

All subjects who fail to complete the study will be categorized by their primary reason for discontinuation and summarized by P3P variant and overall. Disposition of subjects and reasons for withdrawal will also be summarized separately. Supportive listings will be provided.

The number and percent of randomized subjects with protocol deviations and the number of protocol deviations will be summarized by P3P variant and overall, broken down by main deviation category (major/minor) and sub-categories in the randomized population. Subjects will be counted once per deviation category, and can be counted for more than one deviation category.

Supportive listing will be provided, including any additional comments for tests that are not performed to be included on the listings of individual data.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.1.1	Reason for Screen Failure – Screened Population
15.2.2.1	Summary of Subject Disposition – Safety Population
15.2.2.2	Summary of Reasons for Discontinuations – Randomized Population
15.2.3.1	Summary of Protocol Deviations – Randomized Population
LISTINGS	
15.1.1.1	Listing of Inclusion/Exclusion Criteria – Screened Population
15.1.2.1	Listing of Subject Disposition and Assignment to Analysis Sets – Randomized Population
15.1.3.1	Listing of Protocol Deviations – Randomized Population
15.1.3.2	Listing of Subjects and Observations Excluded from the PK Population and PK Analysis – Randomized Population
16.1.1	Listing of Randomization Scheme and Codes

12.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Safety, Randomized and PK populations, and listed for the Safety population.

The demographic variables age, sex, ethnicity, and BMI will be summarized by P3P variant and overall.

Demographics will be tabulated overall, by the sex stratification factor, and by product exposure category as specified in Section 12.1.1 "Stratified Presentation".

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

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.4.2	Summary of Demographics and Other Baseline Characteristics – Randomized Population
15.2.4.3	Summary of Demographics and Other Baseline Characteristics – PK Population
15.2.4.4	Summary of Demographics and Other Baseline Characteristics By Sex – Safety Population
15.2.4.5	Summary of Demographics and Other Baseline Characteristics By Sex– Randomized Population
15.2.4.6	Summary of Demographics and Other Baseline Characteristics By Sex– PK Population
15.2.4.7	Summary of Demographics and Other Baseline Characteristics By Product Exposure Category – Safety Population
15.2.4.8	Summary of Demographics and Other Baseline Characteristics By Product Exposure Category – Randomized Population
15.2.4.9	Summary of Demographics and Other Baseline Characteristics By Product Exposure Category – PK Population
LISTINGS	
15.1.4.1	Listing of Demographics – Randomized Population

12.3.1 Medical History and Concomitant Diseases

Medical history is defined as any condition that started and ended prior to the ICF signature at V1. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and listed separately by P3P variant, System Organ Class (SOC) and Preferred Term (PT) within SOC.

A concomitant disease is defined as any condition that is either detected or is still ongoing at the time of ICF signature Concomitant disease will be coded using MedDRA version 22.0 and listed separately by P3P variant, SOC and PT within SOC.

Partial dates will not be imputed, but assumptions will be made as follows to assign to either medical history or concomitant diseases:

Date information	Assign as
Missing stop date	Concomitant disease
Partial date, e.g., --May2019, 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., --May2019, or -----2019. If month and/or year is earlier than the month and/or year of Screening.	Medical history

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.5.1	Summary of Medical History – Safety Population
15.2.6.1	Summary of Concomitant Diseases – Safety Population
LISTINGS	
15.1.5.1	Listing of Medical History – Safety Population
15.1.6.1	Listing of Concomitant Disease– Safety Population

12.3.2 Tobacco and nicotine containing products use history and habits

All data collected at Screening about tobacco and nicotine containing products use history and habits as described in Table 11 will be summarized.

Table 14: Tobacco and nicotine containing products use history – List of Questions

1. Have you smoked for at least the past 3 consecutive years?
2. How many years have you smoked?
3. On average, how many cigarettes per day have you smoked over the last 3 months?
3b. Of these, on average, per day, how many were menthol cigarettes?
4. On average, how many cigarettes per day have you smoked since you started smoking?
5. Is the variant of brand you are currently using most often menthol or not
6. Have you used any of the following tobacco/nicotine containing products over the last year? a) Pipe b) Hookah c) Heatnotburn Products d) e-cigarette e) Snuff or chewing tobacco

f) Nicotine Replacement Therapy (e.g., patches, gum)
6b Have you used any of the following tobacco/nicotine containing products over the last 7 days? a) Pipe b) Hookah c) Heatnotburn Products d) e-cigarette e) Snuff or chewing tobacco f) Nicotine Replacement Therapy (e.g., patches, gum)
7. During your working hours, on average, how often can you take a break for smoking a cigarette?
8. What are three occasions on which you were using P3P the most during the last month? a) At home, indoors b) At home, outdoors (e.g. garden, balcony) c) In areas where I don't normally smoke (e.g. at my desk at place of work) d) In a designated outdoor smoking area at my place of work e) In a designated indoor smoking area at my place of work f) In a designated indoor or outdoor smoking area (e.g. terrace) in a bar, restaurant, cafe or nightclub g) In public areas (e.g. in the street, in a park) h) At a friend or colleague's home i) At a family member's home j) In the car

Answers to questions 2 to 4 will be considered continuous, all others will be summarized using frequencies. Data will be listed and summarized as presented in the below outputs:

TFL number	Title
TABLES	
15.2.7.1	Summary of Tobacco and nicotine containing products use history and habits –(Q2 to Q4) - Safety Population
15.2.7.2	Summary of Tobacco and nicotine containing products use history and habits –(Q1, Q5-Q8) - Safety Population
LISTINGS	
15.1.7.1	Listing of Tobacco and nicotine containing products use history and habits– Safety Population

12.3.3 Other Data

Other data collected at Screening and/or Admission prior to first P3P product use will be listed by P3P variant and subject. These data are as follows:

- Urine cotinine test
- Urine pregnancy test
- Chest x-ray

- Urine drug screen
- Serology
- Alcohol breath test
- Product Test and Demonstration

ECG, Spirometry, obtained at Screening and/or admission will be presented with data obtained post P3P product use.

The data will be presented in the below outputs:

TFL number	Title
LISTINGS	
15.1.7.2	Urine cotinine test, Urine pregnancy test, Chest x-ray, Urine drug screen, Alcohol breath test, Serology – Safety Population
15.1.7.3	Product Test and Demonstration – Safety Population

12.4 Extent of Exposure (Product Consumption)

The number and percentage of subjects using ≤5/Day, >5-10 /Day, or >10 P3P /Day P3P products per product exposure period (Table 7) and overall will be summarized per product variant for the safety population (By Variant and Total) and by Sex.

Descriptive statistics of the daily product use considered as a continuous variable will be presented as well.
Details of the exposure to product during the on-site period use will be listed by P3P variant for the Safety population.

Listings of average daily exposure by visit period will be provided.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.8.1	Descriptive Statistics of Product Exposure Category by Period - Safety Population
15.2.8.2	Descriptive Statistics of Product Exposure Category by Period and by Exposure Category - By Sex - Safety Population
15.2.8.3	Descriptive Statistics of Product Exposure by Period - Safety Population
15.2.8.4	Descriptive Statistics of Product Exposure by Period - By Sex – Safety Population
LISTINGS	
15.1.8.1	Average Daily Exposure to Product by Period – Randomized Population

12.5 Planned Statistical Analyses

12.5.1 Primary Analyses of PK parameters

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

The same ANCOVA analysis will be performed for the $AUC_{(0\text{-}4h)}$ and C_{max} derived using uncorrected concentrations.

LS means for each product will be back-transformed by exponentiation and will be tabulated together with the ratio (P3P-2mg:P3P-1mg) and 95% CI.

In addition, least square mean ratio and 95% confidence intervals of Day 30 versus Day 1 will be provided by variant using an ANOVA model for the difference Day 30 – Day 1 in the natural logarithmic scale endpoints; the ANOVA model will have variant and sex as factors. LS means for each product will be back-transformed by exponentiation.

The geometric CV will also be presented as $CV(\%) = 100\sqrt{(e^{MSE} - 1)}$, where MSE is the mean square error of the fitted model residual.

Descriptive statistics for t_{max} will be provided by P3P variant, the p-value resulting from the non-parametric between-group comparison (Wilcoxon Rank Sum Test) will be reported. The Hodges-Lehman estimate for the between-group difference in median will be reported together with its 95% CI.

Descriptive statistics will be presented by sex (male or female) and by product exposure category.

For t_{max}, descriptive statistics by sex and product exposure will also be provided.

To better understand the impact of the higher than expected T_0 values, a sensitivity analysis of the Background-Corrected and Uncorrected $AUC_{(0\text{-}4h)}$ and C_{max} will be performed where data for subjects with their T_0 value >5% of their C_{max} value will be excluded from the analysis.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.9.1	Descriptive Statistics of Background-Corrected and Uncorrected Pharmacokinetic Parameters of Nicotine ($AUC_{(0-4h)}$ and C_{max}) at Day 1 and Day 30 – PK Population
15.2.9.2	Analysis of Background-Corrected and Uncorrected Pharmacokinetic Parameters of Nicotine ($AUC_{(0-4h)}$ and C_{max}) at Day 30 and at Day 30 relative to Day 1– PK Population
15.2. 9.3	Descriptive Statistics of Background-Corrected and Uncorrected Pharmacokinetic Parameters of Nicotine ($AUC_{(0-4h)}$ and C_{max}) at Day 1 and Day 30 by Sex– PK Population
15.2. 9.4	Descriptive Statistics of Background-Corrected and Uncorrected Pharmacokinetic Parameters of Nicotine ($AUC_{(0-4h)}$ and C_{max}) at Day 1 and Day 30 by Product Exposure Category– PK Population
15.2.10.1	Descriptive Statistics of Background-Corrected and Uncorrected t_{max} at Day 1 and Day 30 - PK Population
15.2. 10.2	Analysis of Background-Corrected and Uncorrected t_{max} at Day 1 and Day 30 – PK Population
15.2.10.3	Descriptive Statistics of Background-Corrected and Uncorrected t_{max} at Day 1 and Day 30 – by Sex - PK Population
15.2.10.4	Descriptive Statistics of Background-Corrected and Uncorrected t_{max} at Day 1 and Day 30 – By Product Exposure Category – PK Population
15.2. 11.1	Sensitivity Analysis of Background-Corrected and Uncorrected Pharmacokinetic Parameter of Nicotine ($AUC_{(0-4h)}$ and C_{max}) at Day 1 and Day 30 – PK Population
FIGURES	
15.3.1.1	Pharmacokinetic Parameters of Nicotine By P3P variant – PK Population
LISTINGS	
15.1.9.1	Listing of Background-Corrected Pharmacokinetic Parameters of Nicotine – PK Population
15.1.10.1	Listing of Background- Uncorrected Pharmacokinetic Parameters of Nicotine – PK Population

Pharmacokinetic Profiles

Geometric mean (95% CI) profiles, spaghetti plots of individual PK profiles for each subject will also be presented by timepoint.

For the analysis and graphical presentation of plasma concentrations, the nominal timepoints will be used. Plasma concentration data will also be listed along with the details of the actual collection times.

TFL number	Title
TABLES	
15.2.12.1	Descriptive Statistics of Background-Corrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint– PK Population
15.2.12.2	Descriptive Statistics of Uncorrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint– PK Population
15.2.12.3	Descriptive Statistics of Background-Corrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint by Sex – PK Population
15.2.12.4	Descriptive Statistics of Background-Corrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint by Product Exposure Category – PK Population
15.2.12.5	Descriptive Statistics of Uncorrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint by Sex – PK Population
15.2.12.6	Descriptive Statistics of Uncorrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint by Product Exposure Category – PK Population
FIGURES	
15.3.2.1	Background-Corrected Plasma Nicotine Concentration-Time Profiles at Day 1 and Day 30- Linear-– PK Population
15.3.2.2	Uncorrected Plasma Nicotine Concentration-Time Profiles at Day 1 and Day 30–Linear- PK Population
15.3.2.3	Background-Corrected Plasma Nicotine Concentration-Time Profiles at Day 1 and Day 30- Semi-Log-– PK Population
15.3.2.4	Uncorrected Plasma Nicotine Concentration-Time Profiles at Day 1 and Day 30–Semi-Log- PK Population
15.3.2.5	Individual Background-Corrected Plasma Nicotine Concentration-Time Profile at Day 1 and Day 30- Linear-– PK Population
15.3.2.6	Individual Uncorrected Plasma Nicotine Concentration-Time Profile at Day 1 and Day 30- Linear-– PK Population
15.3.2.7	Individual Background-Corrected Plasma Nicotine Concentration-Time Profile at Day 1 and Day 30- Semi-Log-– PK Population
15.3.2.8	Individual Uncorrected Plasma Nicotine Concentration-Time Profile at Day 1 and Day 30- Semi-Log-– PK Population
LISTINGS	
15.1.12.1	Listing of Individual Background-Corrected and Uncorrected Plasma Nicotine Concentrations

12.5.2 Secondary Analyses

12.5.2.1 VAS Craving score

At Day 30, an analysis of covariance (ANCOVA) will be performed on the AUC for the VAS craving score over the duration 0-4h post T_0 denoted $AUC_{VAS\ Craving\ (0\text{-}4h)}$. The model will have P3P variant and sex as factors and Day 1 value as covariate. Comparisons between variants will be performed and LSmeans differences between variant reported with their 95% CI. LSMeans and 95% CI for the $AUC_{VAS\ Craving\ (0\text{-}4h}$ by variant will also be reported.

Changes from baseline at Day 30 in $AUC_{VAS\ Craving\ (0\text{-}4h)}$ will also be analyzed in an ANOVA model with variant and sex as factors. Within-group changes from baseline will be estimated using LSMeans and 95% CI.

Descriptive Statistics of $AUC_{VAS\ Craving\ (0\text{-}4h)}$ at Day 1 and Day 30 and Change from Day 1 at Day 30 Overall; By Sex and By Exposure Category will be provided.

VAS craving score at Day 1 and Day 30 and changes from Day 1 value will be summarized in a descriptive manner by timepoint and P3P variant.

TFL number	Title
TABLES	
15.2.13.1	Descriptive Statistics of $AUC_{VAS\ Craving\ (0\text{-}4h)}$ at Day 1 and Day 30 and Change from Day 1 at Day 30 – Randomized Population
15.2.13.2	Analysis of $AUC_{VAS\ Craving\ (0\text{-}4h)}$ at Day 1 and Day 30 and Change from Day 1 at Day 30 – Randomized Population
15.2.13.3	Descriptive Statistics of $AUC_{VAS\ Craving\ (0\text{-}4h)}$ at Day 1 and Day 30 and Change from Day 1 at Day 30 – By Sex - Randomized Population
15.2.13.4	Descriptive Statistics of $AUC_{VAS\ Craving\ (0\text{-}4h)}$ at Day 1 and Day 30 and Change from Day 1 at Day 30 – By Product Exposure Category - Randomized Population
15.2.13.5	Descriptive Statistics of VAS craving score at Day 1 and Day 30 and Change from Day 1 at Day 30 by Timepoint – Randomized Population
15.2.13.6	Descriptive Statistics of VAS craving score at Day 1 and Day 30 and Change from Day 1 at Day 30 by Timepoint by Sex – Randomized Population
15.2.13.7	Descriptive Statistics of VAS craving score at Day 1 and Day 30 and Change from Day 1 at Day 30 by Timepoint by Product Exposure Category – Randomized Population
FIGURES	
15.3.3.1	VAS Craving Score Profiles By Timepoint at Day 1 and Day 30 – Randomized Population
15.3.3.2	Individual VAS profiles – Randomized Population

TFL number	Title
LISTINGS	
15.1.13.1	Listing of $AUC_{VAS\ Craving\ (0\text{-}4h)}$
15.1.13.2	Listing of VAS craving scores

12.5.2.2 Sensory Questionnaire

Descriptive statistics for the 8 items of the questionnaire on a 7-point scale will be provided by group at Day 1 and Day 30. Data will not be reported by category; this data on a 7-point scale will be considered continuous.

TFL number	Title
TABLES	
15.2.14.1	Descriptive Statistics of Each Item of Sensory Questionnaire (Day 1 and Day 30 and Change from Day 1 at Day 30) (By Variant and Total) – Randomized Population
15.2.14.2	Descriptive Statistics of Each Item of Sensory Questionnaire by Timepoint (Day 1 and Day 30 and Change from Day 1 at Day 30) – By Sex - Randomized Population
15.2.14.3	Descriptive Statistics of Each Item of Sensory Questionnaire (Day 1 and Day 30 and Change from Day 1 at Day 30) – By Product Exposure Category - Randomized Population
LISTINGS	
15.1.14.1	Listing of Sensory Questionnaire Results

12.5.2.3 ABOUT™-Product Experience Questionnaire

The questionnaire which consists of multi-item scales and two single-item scales will be listed and summarized by variant and by stratification factor (sex) for the PK populations.

At Day 30, an ANCOVA model will be used to estimate the mean P3P-2mg:P3P-1mg difference by subscale of the ABOUT™-Product Experience Questionnaire; the model will include P3P variant and sex as factors and value of the subscale score at Day 1 as covariate.

LS means for each variant with 95% interval estimate will be presented in the tables together with the LS mean between-variant difference and 95% confidence interval.

Within-group comparisons between Day 30 and Day 1 will be performed on the basis of an ANOVA model with sex and product exposure category as factors.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.15.1	Descriptive Statistics of ABOUT™-Product Experience Questionnaire Subscales at Day 1 and Day 30 and Change from Day 1 at Day 30 - Randomized Population
15.2.15.2	Analysis of ABOUT™ Product Experience Questionnaire Subscales at Day 30 and Change from Day 1 at Day 30 - Randomized Population
15.2.15.3	Descriptive Statistics of ABOUT™ Product Experience Questionnaire Subscales at Day 1 and Day 30 and Change From Day 1 at Day 30 by Sex – Randomized Population
15.2.15.4	Descriptive Statistics of ABOUT™ Product Experience Questionnaire Subscales at Day 1 and Day 30 and Change From Day 1 at Day 30 by Product Exposure Category – Randomized Population
15.2.15.5	Descriptive Statistics of ABOUT™ Product Experience Questionnaire Individual Questions at Day 1 and Day 30 and Change from Day 1 at Day 30 – Randomized Population
LISTINGS	
15.1.15.1	Listing of ABOUT™ Product Experience Questionnaire Results

12.5.3 Product acceptance and puffing/inhalation behavior

12.5.3.1 Product Acceptance Questionnaire

The data will be presented in the below outputs in a descriptive manner:

Answers to questions 1 to 4 will be considered continuous while anwers to questions 5 and 6 will be presented using frequencies.

TFL number	Title
TABLES	
15.2.16.1	Descriptive Statistics of Product Acceptance at Day 1 and Day 30 and Change from Day 1 at Day 30 (Questions 1 to 4)– Randomized Population
15.2.16.2	Descriptive Statistics of Product Acceptance at Day 1 and Day 30 (Question 5 and 6)– Randomized Population
15.2.16.3	Descriptive Statistics of Product Acceptance (Question 5) – Shift Table from Day 1 to Day 30– Randomized Population
15.2.16.4	Descriptive Statistics of Product Acceptance at Day 1 and Day 30 and Change from Day 1 at Day 30 (Questions 1 to 4) – By Sex - Randomized Population

TFL number	Title
15.2.16.5.	Descriptive Statistics of Product Acceptance at Day 1 and Day 30 (Question 5 to 6)– By Sex- Randomized Population
15.2.16.6	Descriptive Statistics of Product Acceptance at Day 1 and Day 30 and Change from Day 1 at Day 30 (Questions 1 to 4) – By Product Exposure Category- Randomized Population
15.2.16.7	Descriptive Statistics of Product Acceptance at Day 1 and Day 30 (Question 5 to 6) – ByProduct Exposure Category- Randomized Population
LISTINGS	
15.1.16.1	Listing of Product Acceptance Results

12.5.3.2 Puffing/Inhalation behavior

Descriptive data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.17.1	Descriptive Statistics of Puffing Inhalation Behavior Evaluated By Site Staff at Day 1 and Day 30 – Randomized Population
15.2.17.2	Descriptive Statistics of Puffing Inhalation Behavior Evaluated By Site Staff - Shift Table From Day 1 to Day 30 – Randomized Population
15.2.17.3	Descriptive Statistics of Puffing Inhalation Behavior Evaluated By Subject at Day 2, Day 7, Day 15, Day 22 and Day 29 – Randomized Population
15.2.17.4	Descriptive Statistics of Puffing Inhalation Behavior Evaluated By Subject - Shift Table From Day 2 to Day 7, Day 15, Day 22 and Day 29 – Randomized Population
15.2.17.5	Descriptive Statistics of Puffing Inhalation Behavior Evaluated By Site Staff at Day 1 and Day 30 - By Product Exposure Category – Randomized Population
15.2.17.6	Descriptive Statistics of Puffing Inhalation Behavior Evaluated By Subject at Day 2, Day 7, Day 15, Day 22 and Day 29 - By Product Exposure Category – Randomized Population
LISTINGS	
15.1.17.1	Listing of Puffing/Inhalation Behavior (Site) Results
15.1.17.2	Listing of Puffing/Inhalation Behavior (Subject) Results

12.5.4 Nicotine/Tobacco product use

The following variables:

- Average Cigarettes smoked per day during a period
- Change from baseline in average number of cigarettes used per day during a period

- Average Heat not burn and/or smokeless tobacco products used per day during a period
- Average Other tobacco products (pipe, cigar, cigarillos, chewable…) used per day during a period
- Average occasions Electronic Cigarette used per day during a period
- Percentage (%) of P3P used during a period with % P3P = 100* number of P3P/(number of P3P and CC)
- Percentage of subjects having used any Nicotine Replacement Therapies during a period

will be summarized in a descriptive manner for each period being the time interval between 2 consecutive visits and also for the complete exposure period.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.18.1	Descriptive Statistics of Average Cigarettes smoked /day - By Period – Safety Population
15.2.18.2	Descriptive Statistics of Average Cigarettes smoked /day By Product Exposure Category (≤5 P3P/day, >5 – 10 P3P/day, >10 P3P/day) - By Period– Safety Population
15.2.18.3	Descriptive Statistics of Change from Baseline in Average Cigarettes smoked /day - By Period– Safety Population
15.2.18.4	Descriptive Statistics of Average Heat not burn and/or smokeless tobacco products used /day - By Period – Safety Population
15.2.18.5	Descriptive Statistics of Average Other tobacco products (pipe, cigar, cigarillos, chewable…) used/day - By Period – Safety Population
15.2.18.6	Descriptive Statistics of Average occasions Electronic Cigarette used /day - By Period – Safety Population
15.2.18.7	Descriptive Statistics of Percentage (%) of P3P use - By Period – Safety Population
15.2.18.8	Percentage of subjects having used any Nicotine Replacement Therapies – By Period
LISTINGS	
15.1.18.1	Listing of Nicotine/Tobacco product use - By Period

12.5.5 Biomarkers of Exposure in Urine

Urinary concentrations adjusted for creatinine of biomarkers of exposure : Nicontine Equivalents (NEQ), total NNAL and CEMA will be considered log-normally distributed and summarized as described in section 12.1.3. The number and percent of values below LLOQ or above ULOQ will be presented in each summary table.

For each timepoint (Day 7, Day 15, Day 22, Day 29), the values and percent changes from baseline (Day -1) in the concentration adjusted for creatinine of NEQ, total NNAL and CEMA will be summarized by P3P variant, and by product use category.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.19.1	Descriptive Statistics for Biomarkers of Exposure in Urine and Percent change from baseline - By Timepoint– Randomized Population
15.2.19.2	Descriptive Statistics for Biomarkers of Exposure in Urine and Percent Change from Baseline - By Timepoint – By Product Exposure Category - Randomized Population
15.2.19.3	Descriptive Statistics for Biomarkers of Exposure in Urine and Percent Change from Baseline - By Timepoint – By Sex - Randomized Population
LISTINGS	
15.1.19.1	Listing of Biomarkers of Exposure in Urine – By Timepoint - Results

12.5.6 Tobacco and nicotine containing product dependence

The level of perceived dependence associated with tobacco and nicotine-containing product use, summarized by the total score derived from the ABOUT^{TM}- Dependence questionnaire as well as by 3 domain scores will be described.
The individual questions (3c, 3d, 4i, 4j) which are not part of one of the domain scores will only be listed in 15.1.20.1.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.20.1	Descriptive Statistics of ABOUT^{TM}- Dependence questionnaire - Total and By Domain – Baseline, Day 30 and change from baseline – Randomized Population
15.2.20.2	Descriptive Statistics of ABOUT^{TM}- Dependence questionnaire – - Total and By Domain – Baseline, Day 30 and Change From Baseline at Day 30 - By Product Exposure Category - Randomized Population
LISTINGS	
15.1.20.1	Listing ABOUT^{TM}- Dependence questionnaire Results

12.5.7 CYP2A6

CYP2A6 activity at Day 1 (baseline) and Day 30 and change from baseline in CYP2A6 will be summarized by P3P variant and analyzed as a log-transformed variable, by sex and by product exposure category in the randomized population.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.21.1	Descriptive Statistics of CYP2A6 activity – Randomized Population
15.2.21.2	Descriptive Statistics of CYP2A6 activity – By Sex - Randomized Population
15.2.21.3	Descriptive Statistics of CYP2A6 activity – By Product Exposure - Randomized Population
LISTINGS	
15.1.21.1	Listing of CYP2A6 Results

12.5.8 Weighing of P3P Products

For each timepoint (Day 1 and Day 30), the weight difference of P3P before and after use will be derived and presented by P3P variant, by sex and by product exposure category.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.22.1	Descriptive Statistics of Weight of P3P before and after use – Day 1 and Day 30 - PK Population
15.2.22.2	Descriptive Statistics of Weight P3P of before and after use – Day 1 and Day 30 – By Sex - PK Population
15.2.22.3	Descriptive Statistics of Weight of P3P before and after use – Day 1 and Day 30 – By Product Exposure Category - PK Population
FIGURES	
15.3.4.1	Scatter Plot of PK $AUC_{(0-4h)}$ versus P3P Weight difference By Puffing Behavior – Day 1 and Day 30 – PK Population
LISTINGS	
15.1.22.1	Listing Results of Weight of P3P before and after use – Day 1 and Day 30

12.5.9 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, physical examination, respiratory symptoms (cough assessment VAS and Likert scales).

The primary analysis of Safety parameters will be conducted on the Safety population. All safety tables will be presented by variant and overall.

12.5.9.1 Safety Reporting

An exposure emergent AE is defined as an AE that occurs after first 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.

Any AEs which occur after ICF signature will be captured by the site collaborators and assessed by the Investigator or designee in order to establish relationship or relatedness in respect to study procedures. The AE listings will include all AEs captured in the database at any time during the study (including those from subjects who were not in the safety population). All AEs occurring after the product test use will be included in the summary tables. During the screening period prior to the first product use, only study procedure related AEs will be listed.

AEs reported from enrolled subjects, but who did not start use on day 1 or later will be summarized in a separate listing: “Enrolled but not started randomized product use AEs”. Furthermore AEs reported after discharge on Day 30 are summarized in a separate listing ‘Safety follow-up AEs’.

If there are more than 10 AEs, the tables will also be split by product exposure period. The product exposure periods will be defined as below

Partial dates will not be imputed, but assumptions will be made as follows to assign to exposure-emergent or not:

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 first product use	Exposure-emergent
Partial date, e.g., --May2012, or -----2011. If month and/or year is earlier than the month and/or year of first product use	Not exposure-emergent

If exposure emergent adverse events cannot be attributed to P3P due to e.g. missing start time, the worst case principle will be applied : i.e. the event will be allocated to P3P use.

12.5.9.2 Adverse Events

A general summary table of AEs will be presented by P3P variant and overall, including:

- The number of events and the number and percentage of subjects reporting at least one AE.
- The number of events and the number and percentage of subjects reporting at least one SAE
- The number of events and the number and percentage of subjects reporting at least one investigational product –related AE, broken down by product relatedness (related to P3P) and expectedness (expected, not expected).
- The number of events and the number and percentage of subjects reporting at least one AE related to study procedure.
- 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.
- The number of events and the number and percentage of subjects reporting at least one AE leading to any action taken, broken down by action taken related to the product (combining the following items: product use interrupted, product use reduced, product use stopped), treatment given and any other action taken
- The number of events and the number and percentage of subjects reporting at least one AE leading to study discontinuation.

Additional summary tables of AEs will be presented by P3P variant (and period if more than 10 AEs) and overall, 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 22.0):

- The number of events and the number and percentage of subjects reporting at least one AE.
- The number of events and the number and percentage of subjects with at least one AE related to investigational product.
- The number of events and the number and percentage of subjects with at least one expected AE.

- The number of events and the number and percentage of subjects with at least one AE leading to product discontinuation.
- The number of events and the number and percentage of subjects with at least one AE related to study procedure.
- The number of events and the number and percentage of subjects with at least one AE by severity (mild, moderate, severe)

If a subject has more than one occurrence of the same AE, the subject will be counted only once within a PT for each P3P variant, 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.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.23.1	Summary of Adverse Events – Safety Population
15.2.23.2	Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.23.3	Summary of Adverse Events Related to Investigational Product by System Organ Class and Preferred Term - Safety Population
15.2.23.4	Summary of Adverse Events Related to Study Procedures by System Organ Class and Preferred Term - Safety Population
15.2.23.5	Summary of Expected Adverse Events by System Organ Class and Preferred Term
15.2.23.6	Summary of Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
15.2.23.7	Summary of Adverse Events Leading to Investigational Product Discontinuation by System Organ Class and Preferred Term – Safety Population
15.2.23.8	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
LISTINGS	
15.1.23.1	Listing of Exposure Emergent Adverse Events
15.1.23.2	Enrolled but not started randomized product use AEs
15.1.23.3	Safety follow-up AEs
15.1.23.4	Listing of AEs leading to study discontinuation

12.5.9.2.1 Serious Adverse Events (Including Deaths)

A general summary table of Serious AEs will be presented by P3P variant and overall, including:

- The number of events and the number and percentage of subjects reporting at least one SAE, broken down by seriousness criteria (results in death, hospitalisation, life-

threatening, congenital anomaly/birth defect, disability/incapacity; important medical event);

- The number of events and the number and percentage of subjects reporting at least one SAE broken down by product relatedness (related, not related);
- The number of events and the number and percentage of subjects reporting at least one SAE broken down by study procedure relatedness (related, not related);
- The number of events and the number and percentage of subjects reporting at least one SAE broken down by expectedness (expected, not expected);
- The number of events and the number and percentage of subjects reporting at least one SAE broken down by severity, including a subject once with worst severity ;
- The number of events and the number and percentage of subjects reporting at least one SAE broken down by action taken related to the product (combining the following items: product use interrupted, product use reduced, product use stopped), treatment given and other action taken;
- The number of events and the number and percentage of subjects reporting at least one SAE leading to study discontinuation;

Additional summary tables of SAEs 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 22.0):

- The number of events and the number and percentage of subjects reporting at least one AE

SAEs will be listed in separate listings by P3P variant.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.24.1	Summary of Serious Adverse Events – Safety Population
15.2.24.2	Summary of Serious Adverse Events by System Organ Class and Preferred Term – Safety Population
LISTINGS	
15.1.24.1	Listing of Serious Adverse Events

12.5.9.3 Investigational Product Events

All events relating to P3P Malfunction and Misuse will be listed for each subject, including event description and onset datetimes.

A summary table of P3P Product Events will be presented by P3P variant and overall, including:

- Number of P3P Product events and the number and percentage of subjects reporting at least one event.
- Number and percentage of subjects with device events linked to an AE

P3P Malfunction and Misuse events and inventory will be listed by P3P variant.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.25.1	Summary of P3P Product events by Subject - Safety Population
15.2.25.2	Summary of P3P Product events by total number of P3P used – Safety Population
15.2.25.3	Summary of P3P Product events leading to an Adverse Event - Safety Population
LISTINGS	
15.1.25.1	Listing of P3P Events
15.1.25.2	Listing of AE related to P3P events

12.5.9.4 Clinical Laboratory Evaluation

Table 15 lists the hematology, clinical chemistry, and urine analysis parameters to be assessed in this study at Screening, Admission, Day 15, and Day 30.

Table 15: List of Laboratory Safety Parameters

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

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the PI and assessed for clinical significance. If the PI considers the abnormal result to be of clinical significance, then it must be recorded as a concomitant disease at Screening, or if not present at Screening, as an AE during the study. If the condition worsens after screening it will be recorded as an AE. Abnormal laboratory test results detected at the Screening Visit whose Common Toxicity Criteria Adverse Event (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. 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 PI to assess abnormal laboratory AEs.

Laboratory data will be summarized and listed at Screening, Day -1, Day 15 and at Day 30 or early termination, together with changes from baseline (last measurement obtained from screening or day -1 measurements). The number and percentage of subjects with:

- normal/low/high values
- clinical interpretation - normal, abnormal not clinically significant/abnormal clinically significant results)
- Severity - normal/abnormal laboratory findings by rating Mild, Moderate, Severe, Life Threatening based on CTCAE 4.0 grading

will be reported at Baseline Day 15 and at Day 30 or early termination, when appropriate.

Shift tables from Baseline for the normal/low/high values will be constructed at Day 15 and at Day 30.

Shift tables from Baseline over the product exposure (any visit post first product exposure) will be contructed for normal, abnormal not clinically significant/abnormal clinically significant results and for normal/abnormal laboratory findings by rating. For the shift table, the most “severe” value obtained during product exposure will be kept using the following order (from least severe to most severe):

Normal < Abnormal not clinically significant <Abnormal clinically significant

Normal<Mild < Moderate < Severe < Life threatening

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

the PI) , the change from baseline and the CTCAE grade. Only CTCAE grades equal or greater than one (Mild) will be presented.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.26.1	Descriptive Statistics of Clinical Chemistry Parameters - Safety Population
15.2.26.2	Summary of Clinical Chemistry Parameters - Safety Population
15.2.26.3	Shift Table of Clinical Chemistry Parameters (Normal/Low/High) - Safety Population
15.2.26.4	Shift Table of Clinical Chemistry Parameters (Severity) - Safety Population
15.2.26.5	Shift Table of Clinical Chemistry Parameters (Clinical interpretation) - Safety Population
15.2.26.6	Descriptive Statistics of Hematology Parameters - Safety Population
15.2.26.7	Summary of Hematology Parameters - Safety Population
15.2.26.8	Shift Table– of Hematology Parameters (Low/Normal/High) - Safety Population
15.2.26.9	Shift Table of Hematology Parameters (Severity) - Safety Population
15.2.26.10	Shift Table of Hematology Parameters (Clinical Interpretation) - Safety Population
15.2.26.11	Descriptive Statistics of Urinalysis Parameters - Safety Population
15.2.26.12	Summary of Urinalysis Parameters Parameters - Safety Population
15.2.26.13	Shift Table of Urinalysis Parameters (Normal/Low/High) - Safety Population
15.2.26.14	Shift Table of Urinalysis Parameters (Severity) - Safety Population
15.2.26.15	Shift Table of Urinalysis Parameters (Clinical Interpretation) - Safety Population
LISTINGS	
15.1.26.1	Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades
15.1.26.2	Listing of Hematology Data, Shift, Changes from Baseline and CTCAE grades
15.1.26.3	Listing of Urinalysis Data, Shift, Changes from Baseline and CTCAE grades

12.5.9.5 Vital Signs, Physical Examination and Other Observations Related to Safety

12.5.9.5.1 Prior and Concomitant Medication

Prior medication is defined as any medication taken within 4 weeks prior to Screening. Any medication which was started prior to the Screening Visit and is still being taken by the subject will be considered as concomitant medication. Medication initiated after the Screening Visit is also referred to as concomitant medication.

All medications will be listed using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization - Drug Dictionary Enhanced [WHO-DDE] March 2015 C format). A flag will be presented on the listing indicating whether the medication is prior or concomitant. Partial dates will not be imputed, but assumptions will be made as follows to assign to either prior or 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

Prior and Concomitant medications will be summarized for the Safety population (By Variant and Overall) 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. Listings will display original dates (no imputation).

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.27.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.27.2	Summary of Prior Medication by Preferred Drug Name – Safety Population
15.2.27.3	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 – Safety Population
15.2.27.4	Summary of Concomitant Medication by Preferred Drug Name – Safety Population
LISTINGS	
15.1.27.1	Listing of Prior and Concomitant Medication

12.5.9.5.2 Physical Examination

Physical examination data recorded during the study will be listed by P3P variant. Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. Number of subjects (%) with normal, abnormal, and abnormal clinically significant results will be tabulated by body systems by visit.
Height recorded at the Screening visit and Body weight recorded at Screening visit, admission and discharge will also be listed. Descriptive statistics of body weight, and body height will be tabulated.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.28.1	Summary of Weight and Height Measurements – Safety Population
15.2.28.2	Summary of Physical Examination of Body Systems – Safety Population
15.2.28.3	Shift Table of Physical Examination – Safety Population
LISTINGS	
15.1.28.1	Listing of Physical Examination Findings, and Changes from Screening

12.5.9.5.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate and respiratory rate measured during the study will be listed by P3P variant and study day.

Descriptive statistics will be presented for values and changes from baseline (baseline being the last measurement obtained prior to product test) 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.

Shift tables from baseline over the product exposure (any visit post first product exposure) will be contructed for normal, abnormal not clinically significant/abnormal clinically significant vital signs results. For the shift table, the most "severe" value obtained during product exposure will be kept using the following order (from least severe to most severe):

Normal < Abnormal not clinically significant <Abnormal clinically significant

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.29.1	Descriptive Statistics of Vital Signs– Safety Population
15.2.29.2	Summary of-Vital Signs – Safety Population
15.2.29.3	Shift Table of Vital Signs – Safety Population

TFL number	Title
LISTINGS	
15.1.29.1	Listing of Vital Signs Data and Changes from Baseline

12.5.9.5.4 Spirometry

Spirometry parameters assessed during the study include:

- Measured forced expiratory volume in 1 second (FEV_1)
- Measured forced vital capacity (FVC)
- FEV_1/FVC
- Percent of predicted FEV_1 (% pred)
- Percent of predicted FVC (% pred)
- FEF 25
- FEF 25 % predicted
- FEF 75
- FEF75 % predicted
- FEF 25-75
- FEF 25-75 % predicted

Measurement interpretation (categories: normal, abnormal not clinically significant, abnormal clinically significant) is collected by timepoint.
The above data are collected at all study day. At Screening, data are collected prior and post-bronchodilator, also including the brand (trade) name and dose of the bronchodilator.

At Day -1 spirometry will be performed before and after product use.

At Day 1 and 2 spirometry will be performed before product use and at the end of the daily product use.

Spirometry data values and normality evaluation will be listed by P3P variant and study day. Assessments performed after baseline will be listed together with change from baseline and shift in normality. Spirometry data from subjects who had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for FEV1, FEV1 % predicted, FVC, FVC % predicted, FEF 25, FEF 25 % predicted, FEF 75, FEF75 % predicted, FEF 25-75, FEF 25-75 % predicted, FEV1/FVC by study day by P3P variant. Spirometry data will be summarized together with changes from baseline (baseline being the last measurement obtained prior to product test), and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results.
Shift tables from baseline over the product exposure (any visit post first product exposure) will be contructed for normal, abnormal not clinically significant/abnormal clinically significant spirometry results. For the shift table, the most “severe” value obtained during product exposure will be kept using the following order (from least severe to most severe):

Normal < Abnormal not clinically significant <Abnormal clinically significant

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.30.1	Descriptive Statistics of Spirometry Results- Safety Population
15.2.30.2	Summary of Spirometry Results – Safety Population
15.2.30.3	Shift Table of Spirometry Results) – Safety Population
15.2.30.4	Descriptive Statistics of Spirometry Results- Safety Population – By Product Use Category
LISTINGS	
15.1.30.1	Listing of Spirometry Data and Changes from Baseline

12.5.9.5.5 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces, i.e. not centrally read. These data include the PR, QT, and QT interval corrected using Bazett's formula (QTcB) and Fridericia's formula (QTcF) intervals; QRS duration; heart rate; and normality evaluation (normal, abnormal not clinically relevant, abnormal clinically relevant, together with any PI comments about the abnormality). ECG data values and normality evaluations will be listed by P3P variant and study day together with changes and shift in normality from baseline (Visit 2 Day -1). ECG data from subjects which had significant clinical findings will be highlighted in listings.

Descriptive statistics will be presented for ECG data at each study day by P3P variant and overall. ECG data will be summarized together with changes from baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinical significant results.

A shift table for ECG assessments from baseline to worst assessment post-baseline, including unscheduled visits, will be done. For the shift table, the most "severe" value obtained during product exposure will be kept using the following order (from least severe to most severe):

Normal < Abnormal not clinically significant <Abnormal clinically significant

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.31.1	Descriptive Statistics of ECG Measurements - Safety Population
15.2.31.2	Summary of ECG Measurements – Safety Population
15.2.31.3	Shift of ECG Measurements(Normal/Abnormal no Clinically Significant /Abnormal Clinically Significant) – Safety Population
LISTINGS	

TFL number	Title
15.1.31.1	Listing of ECG Data and Changes from Baseline

12.5.9.5.6 Assessment of Cough

Cough questionnaire is assessed at Day -1, 2, 7, 15, 22, and 29. The number and % of subjects reporting a cough will be summarized by P3P variant. The responses to the individual items, including the VAS evaluating the level of cough bother and 3 Likert scales measuring the intensity, the frequency of cough and the amount of sputum production will be listed and summarized on each day by P3P variant, for all subjects who filled in the questionnaire.

The data will be presented in the below outputs:

TFL number	Title
TABLES	
15.2.32.1	Number and Percentage of Subjects with Cough – Safety Population
15.2.32.2	Summary of VAS Level Cough Bothersome by Timepoint – Safety Population
15.2.32.3	Summary of Intensity, Frequency of Cough and Sputum Production by Timepoint – Safety Population
LISTINGS	
15.1.32.1	Listing of Cough Assessment Results – VAS measurement
15.1.32.2	Listing of Cough Assessment Results - Frequency of Cough and Sputum Production

13 ANALYSIS AND REPORTING

13.1 Interim Analysis

No interim analysis is planned on this study.

13.2 Topline Results

Topline results, composed of key statistics and study results listings, will be made available to PMPSA following database lock and prior to completion of the complete set of TFLs. The following tables, figures, and listings will be made available following database lock:

TFL no.	Title
TABLES	
15.2.4.1	Summary of Demographics and Other Baseline Characteristics – Safety Population
15.2.8.3	Descriptive Statistics of Product Exposure by Period - Safety Population
15.2.9.1	Descriptive Statistics of Background-Corrected and Uncorrected Pharmacokinetic Parameters of Nicotine ($AUC_{(0-4h)}$ and C_{max}) at Day 1 and Day 30 – PK Population
15.2.9.2	Analysis of Background-Corrected and Uncorrected Pharmacokinetic Parameters of Nicotine ($AUC_{(0-4h)}$ and C_{max}) at Day 30 and at Day 30 relative to Day 1– PK Population
15.2.12.1	Descriptive Statistics of Background-Corrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint– PK Population
15.2.12.2	Descriptive Statistics of Uncorrected Plasma Nicotine Concentration at Day 1 and Day 30 by Timepoint– PK Population
15.2.13.2	Analysis of $AUC_{VAS\ Craving\ (0-4h)}$ at Day 1 and Day 30 and Change from Day 1 at Day 30 – Randomized Population
15.2.18.3	Descriptive Statistics of Change from Baseline in Average Cigarettes smoked /day - By Period– Safety Population
15.2.23.1	Summary of Adverse Events – Safety Population
15.2.23.2	Summary of Adverse Events by System Organ Class and Preferred Term – Safety Population
15.2.25.1	Summary of P3P Product events by Subject - Safety Population
15.2.26.2	Summary of Clinical Chemistry Parameters - Safety Population
15.2.26.7	Summary of Hematology Parameters - Safety Population
15.2.26.12	Summary of Urinalysis Parameters - Safety Population
15.2.30.1	Descriptive Statistics of Spirometry Results- Safety Population
FIGURES	
15.3.2.1	Background-Corrected Plasma Nicotine Concentration-Time Profiles at Day 1 and Day 30- Linear-– PK Population
15.3.2.2	Uncorrected Plasma Nicotine Concentration-Time Profiles at Day 1 and Day 30–Linear- PK Population
15.3.3.1	VAS Craving Score Profiles By Timepoint at Day 1 and Day 30 – Randomized Population
LISTINGS	
15.1.23.1	Listing of Exposure Emergent Adverse Events
15.1.23.4	Listing of AEs leading to study discontinuation

13.3 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, randomization code unblinded, 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 RSR.

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

14 DATA PRESENTATION

A separate TFL style guide document will be provided.

15 REFERENCES

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International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

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Jacob P 3rd, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL. Determination of the Nicotine Metabolites Cotinine and Trans-3'-Hydroxycotinine in Biologic fluids of Smokers

and Non-smokers using Liquid Chromatography - Tandem Mass Spectrometry: Biomarkers for Tobacco Smoke Exposure and for Phenotyping Cytochrome P450 2A6 Activity. J Chromatogr B Analyt Technol Biomed Life Sci. 2011 Feb 1;879(3-4):267-276.

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16 APPENDICES

Appendix A – Schedule of Events

	Screening	Admission	Product use period (up to 15 products/day)						Discharge	Early termination	Safety Follow-Up
Visit	**1**	**2**			**3**	**4**	**5**	**6**			
Study day	**-22 to -2**	**-1**	**1**	**2**	**7 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**30 ±2d**		**+14 days**
Informed consent	●										
Information on the risks of smoking/ smoking cessation advice and debriefing on P3P	●	●						●		●	
Inclusion/exclusion criteria [a]	●	●									
Tobacco and nicotine containing products use history and habits	●										
P3P demonstration	●										
Demographics	●										
Medical history/concomitant diseases	●										
Chest X-ray [b]	●										
B: HIV, Hepatitis B and C	●										

	Screening	Admission	Product use period (up to 15 products/day)						Discharge	Early termination	Safety Follow-Up
Visit	**1**	**2**			**3**	**4**	**5**	**6**			
Study day	**-22 to -2**	**-1**	**1**	**2**	**7 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**30 ±2d**		**+14 days**
U: Drug screen	●	●									
U: Cotinine test	●	●									
U: Pregnancy test	●	●				●		●		●	
Alcohol breath test	●	●									
Vital signs [c]	●	●	●	●	●	●	●	●	●	●	
Physical examination	●	●		●	●	●	●		●	●	
Body height, weight and BMI [d]	●	●							●		
Spirometry [e]	●	●	●	●	●	●	●	●	●	●	
Prior/concomitant medication	●	●	●	●	●	●	●	●	●	●	●[f]
B/U: Hematology, clinical chemistry, urinalysis safety panel	●	●				●			●	●	
ECG	●	●	●	●	●	●	●		●	●	
Enrollment		●									
P3P product test [g]		●									

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Visit	**1**	**2**			**3**	**4**	**5**	**6**			
Study day	**-22 to -2**	**-1**	**1**	**2**	**7 ±2d**	**15 ±2d**	**22 ±2d**	**29 ±2d**	**30 ±2d**		**+14 days**
Willing to continue to use P3P for 1 Month (confirmation after product test)		•									
Randomization		•									
B: CYP2A6 activity [h]			•						•		
Overnight nicotine wash-out period [i]		•						•			
P3P single product use for PK assessment [j]			•						•		
Weighing of P3P [k]			•						•		
Collection of used and unused P3P [l]					•	•	•	•		•	
On-site product use (up to 15 P3P)			•	•							
P3P resupply				•	•	•	•				
B: nicotine in plasma [m]			•						•		
U: BoExp [n]		•			•	•	•	•			
B/U: Biobanking			•						•		

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

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

a. Prior to enrollment, at Day -1 the following eligibility criteria will be re-checked: Inclusion criteria: smoking status confirmed by urine cotinine, subject is not planning to quit smoking within 2 months, subject is available for the entire study period and is willing to comply with the study procedures. Exclusion criteria: urine pregnancy test (all females), urine drug screen and alcohol breath test. The following eligibility criteria will only be checked at Day -1: Exclusion criteria: subject has received medication which has an impact on CYP2A6 activity within 14 days or within 5 half-lives of the drug prior to Day -1 (whichever is longer)
b. Pre-study chest X-ray (with anterior-posterior and left lateral views). Available chest computed tomography (CT) or chest magnetic resonance imaging (MRI) results, or radiologist report from an equivalent radiological assessment within 6 months prior to Screening.
c. Systolic and diastolic blood pressure, pulse rate, and respiratory rate. At V2 (Day -1, Day 1 and Day 2) and V6 (Day 30) vital signs are to be checked prior to any product use and at the end of the day/at discharge.
d. Subjects with a BMI < 18.5 kg/m^2 or BMI ≥ 32 kg/m^2 will be excluded. At V2 and V6 weight only will be recorded.
e. Spirometry with and without bronchodilator performed at Screening. Spirometry without bronchodilator performed at the remaining visits. At Day -1, spirometry will be performed before and after product test. At Day 1 and Day 2 spirometry will be performed before product use and at the end of the daily product use.
f. Only medication used for treatment of an AE/SAEs
g. P3P product test using up to 6 P3P products (both P3P-1mg and P3P-2mg) will be conducted at Day -1 after enrollment. A wash-out period from any tobacco/nicotine containing products of at least 4 h prior to product test is needed.
h. Sample taken in the morning prior to product use.
i. Starting on the first day of each confinement period, subjects will abstain from tobacco/nicotine containing products for at least 10 h prior to P3P use for PK assessment on the second confinement day.
j. Use of a single product with puffing depending on the subjects preference (*ad libitum* use) for a duration of up to 15 minutes.
k. Each P3P used for PK assessment should be weighed prior to product use and within 1h after the end of the use.
l. On Day 29 collection of unused P3P should occur right before the start of the 10h wash-out period.
m. A total of 11 blood samples will be taken for PK parameter estimation at Day 1 and Day 30. Three blood samples will be taken prior to the start of product use (T_0) 1 hour ± 5 minutes, 30 minutes ± 5 minutes and 5 minutes ± 2 minutes before T_0. Thereafter in relation to T_0, blood will be drawn at the following time points: after 4 minutes ± 1 minute, after 7 minutes ± 1 minute, after 10 minutes ± 1 minute, after 15 minutes ± 2 minutes, after 30 minutes ± 2 minutes, after 1 hour ± 5 minutes, after 2 hours ± 5 minutes and after 4 hours ± 5 minutes.
n. NEQ,total NNAL and CEMA will be analyzed in spot urine and adjusted for creatinine.

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

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

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