PHILIP MORRIS PRODUCTS S.A.

STATISTICAL ANALYSIS PLAN

A single-center, randomized, controlled, open-label study to investigate the nicotine pharmacokinetic profiles and subjective effects of four variants of Nicotine pouch 1.0 compared to Velo® Ice Cool and Zyn® Cool Mint Mini Dry in healthy smokers

Protocol No: P5-PK-01-EXP

Final Protocol Version 2.0 Date: 07 March 2022

Product Name: Nicotine pouch (NP) 1.0

[redacted]

Final Version 1.0
Date: 21 March 2022

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ABBREVIATIONS

AE	Adverse event
ALQ	Above limit of quantification
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical therapeutic and chemical
ATS	American thoracic society
AUC	Area under the curve
BLQ	Below limit of quantification
BMI	Body mass index
CFR	Code of Federal Regulations
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTMS	Clinical trial management system
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
ERS	European respiratory society
FDA	Federal drug administration
FTND	Fagerström test for nicotine dependence
FVC	Forced vital capacity
GCP	Good clinical practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International conference of Helsinki
IEC	Independent Ethics Committee
KR	Kenward-Roger degrees of freedom
LLOQ	Lower limit of quantification
NCA	Non-compartmental analysis
NP	Nicotine pouches
PES	Product evaluation scale
PK	Pharmacokinetics

PMP	Philip Morris Products
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical analysis system
SDTM	Study data tabulation model
SEM	Standard error of the mean
TFL	Table, listing and figure
ULOQ	Upper limit of quantification
USA	United States of America
VAS	Visual analogue scale

1. INTRODUCTION

This statistical analysis plan (SAP) has been developed to supplement the statistical analyses described in the clinical study protocol (CSP) final version 2.0 dated 07 March 2022.

This current document describes the methodology and considerations of the planned analyses. The current document will be supplemented with a list of all the TFLs for this study and the corresponding shells.

Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses, will be described in the clinical study report (CSR).

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

- Good Clinical Practice (GCP) guidelines E6 (R1)
- International Council on Harmonization (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".
- ICH E9 (R1) addendum on “Estimands and sensitivity analysis in clinical trials”.
- Clinical Study Protocol final version 2.0 dated 07 March 2022.

1.1 Revision History

Version	Date of Revision	Revision
Final version 1.0	21 Mar 2022	Original Version

2. OBJECTIVES AND ENDPOINTS

The estimands requested as per ICH guidelines for all objectives are listed in the protocol under Section 12.

Exploratory Objectives and Endpoints:

The objectives and endpoints of this study are:

1. To describe the plasma concentration-time profile of nicotine and derived pharmacokinetic (PK) parameters of 4 variants of Nicotine pouch (NP) 1.0 nicotine pouches compared to Velo-NP and Zyn-NP in healthy smokers from a 30 minutes product use period.

Endpoints

- Background-corrected maximum plasma concentration [C_{max}]
- Background-corrected time to the maximum concentration [T_{max}]
- Area under the background-corrected concentration-time curve (AUC) from start of product use (T_0), to all subsequent time points and extrapolated to infinity [$AUC_{0\text{-}5min}$, $AUC_{0\text{-}10min}$, $AUC_{0\text{-}15min}$, $AUC_{0\text{-}20min}$, $AUC_{0\text{-}25min}$, $AUC_{0\text{-}30min}$, $AUC_{0\text{-}35min}$, $AUC_{0\text{-}40min}$, $AUC_{0\text{-}1h}$, $AUC_{0\text{-}3h}$, $AUC_{0\text{-}6h}$, $AUC_{0\text{-}infinity}$]

2. To describe pharmacodynamic (PD) effects (subjective effects and related behavioral assessments) of 4 variants of NP 1.0 compared to Velo-NP and Zyn-NP in healthy smokers from a 30 minutes product use period.

Endpoints (Day 1 to Day 3)

- Score of cigarette craving by the visual analog scale (VAS)-craving assessment [VAS-C_{-15min}, VAS-C_{5min}, VAS-C_{10min}, VAS-C_{15min}, VAS-C_{20min}, VAS-C_{25min}, VAS-C_{30min}, VAS-C_{35min}, VAS-C_{40min}, VAS-C_{1h}, VAS-C_{3h}, VAS-C_{6h}]
- Score of "in the moment" product liking by the VAS-liking (in the moment) assessment [VAS-L_{5min}, VAS-L_{10min}, VAS-L_{15min}, VAS-L_{20min}, VAS-L_{25min}, VAS-L_{30min}, VAS-L_{35min}, VAS-L_{40min}, VAS-L_{1h}, VAS-L_{3h}]
- Score of overall product liking by the VAS-liking (overall) assessment
- Score of product satisfaction by the VAS- satisfaction assessment [VAS-S_{5min}, VAS-S_{10min}, VAS-S_{15min}, VAS-S_{20min}, VAS-S_{25min}, VAS-S_{30min}, VAS-S_{35min}, $VASS_{40min}$, VAS-S_{1h}, VAS-S_{3h}, VAS-S_{6h}]
- Score of product intention to use again by the VAS-intention to use again assessment [VAS-ITU_{30min}, VAS-ITU_{3h}]
- Subscale scores from the Product Evaluation Scale (PES)
- Scores from items of the Sensory questionnaire

3. To evaluate the safety and tolerability during the study

Endpoints (from Enrollment to EOS):

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of product events
- Changes in electrocardiogram (ECG) from baseline (heart rate, PR, QRS, QT, QTcF interval)

- Changes in vital signs from baseline (systolic and diastolic blood pressure, pulse rate, and respiratory rate)
- Concomitant medication
- Changes from baseline in clinical chemistry, hematology, and urine analysis safety panel

4. To describe the associations between PK and PD parameters.

Endpoints (Day 1 to Day 3):

- Between the score of "in the moment" product liking by the VAS-liking assessment averaged over the product use period (from T1 to T6) and during the sequence period (T1 to T9) and C_{max}, T_{max}, and $AUC_{0\text{-infinity}}$ PK endpoints
- Between the average score of "in the moment" product satisfaction by the VAS product satisfaction assessment during the sequence's period (from T1 to T11) and C_{max}, T_{max}, and $AUC_{0\text{-infinity}}$ PK endpoints
- Between the score of "in the moment" craving by the VAS-craving assessment averaged during the sequence's period (from T1 to T11) and C_{max}, T_{max}, and $AUC_{0\text{-infinity}}$ PK endpoints
- Between the subscale scores of PES and $AUC_{0\text{-infinity}}$ PK endpoint
- Between the item scores of the Sensory questionnaire and $AUC_{0\text{-infinity}}$ PK endpoint

5. To describe the extent of nicotine extracted during product use from 4 variants of NP 1.0, Velo-NP and Zyn-NP. This objective is not covered within the SAP and the reporting of this objective will be separate from the main CSR.

Endpoint (Day 1 to Day 3)

- Estimated amount of nicotine extracted derived from analysis of nicotine after use.

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

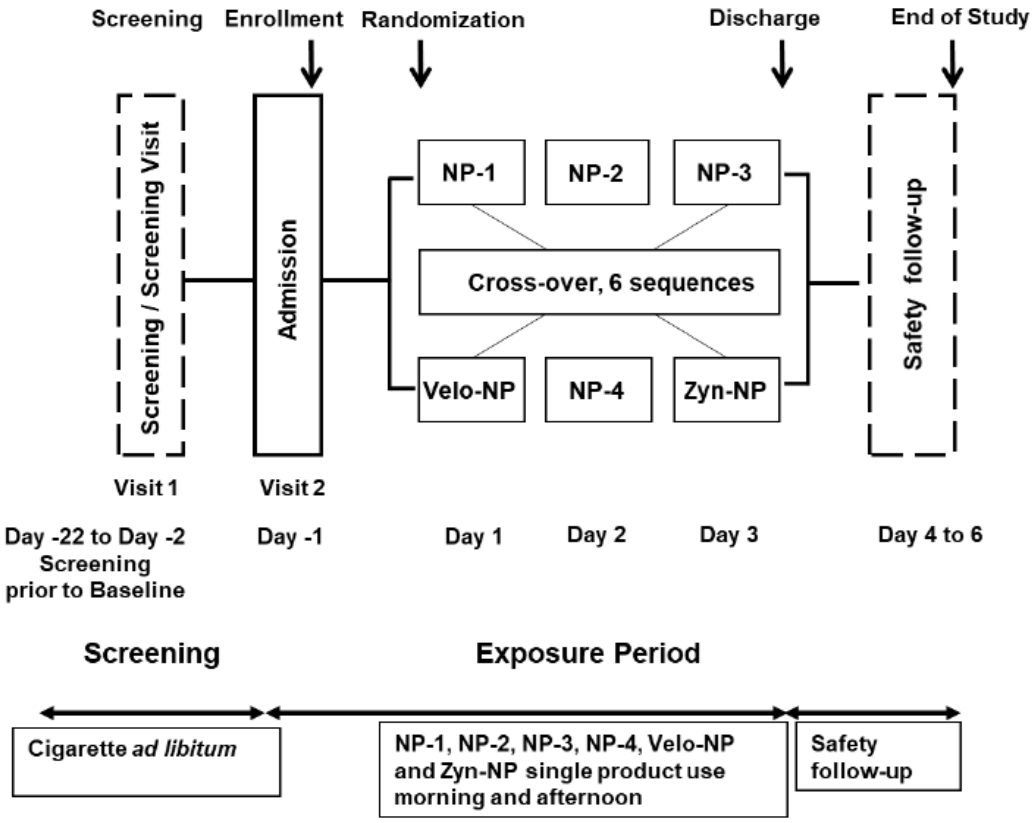
3. INVESTIGATION PLAN

3.1 STUDY DESIGN

This is a single-center, randomized, controlled, open-label, cross-over study in healthy smoking subjects to investigate the nicotine PK profiles of 4 variants of NP 1.0 compared to marketed Velo-NP and Zyn-NP. In addition, PD effects will be evaluated to provide further insights on NP 1.0 product acceptance and abuse liability. The study will be conducted with 6 product use periods and 6 sequences in a Williams design (cross-over).

A Screening Visit will be conducted within 21 days (Day -22 to Day -2) prior to Admission (Day -1) to the investigational site (Figure 1). Subjects will be screened against eligibility criteria.

Figure 1 Study Design



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

On Day -1, enrolled subjects will perform a product test using NP-1 for 30 minutes (± 1 minute). After the product test, subjects not willing and/or not ready to use NP 1.0 during the study will be discontinued from the study, will enter the 3-day Safety follow-up period, and will be replaced.

Subjects willing and ready to use NP 1.0, Velo-NP and Zyn-NP during the study after product test will start their exposure period of 3 days.

Twenty-four (24) subjects will be randomized to 1 of 6 possible sequences of product use on Day 1 to Day 3 with at least 25% of each sex (see Figure 1). The randomization process including the randomization sequences will be documented in the randomization plan.

On Day 1 to Day 3, after at least 8 hours of abstinence from any nicotine/tobacco containing products (nicotine wash-out), subjects will use one NP for 30 minutes (± 1 minute) according to randomized product use sequence in the morning and in the afternoon, by placing the NP between the upper lip and gum. Subjects will complete self-reported assessments of product evaluation, craving, liking, satisfaction, and intent to use again.

The start of the 30 minutes use period will be defined as T_0. T_0 in the morning (T_{0M}) and in the afternoon (T_{0A}) on Day 1 to Day 3 should be approximately at the same time, within a window of ± 30 minutes. Venous blood samples will be obtained according to the standard operating procedures (SOPs) at the investigational site.

On Day 1, 12 blood samples will be collected for determination of nicotine concentration at the following time points in relation to T_0 with a time window as indicated in brackets:

Morning prior to T_{0M} and afternoon prior to $T_{0A:}$:

- T-1: 5 minutes (± 1 minute)

After T_{0M} and $T_{0A:}$

- T1 after 5 minutes (± 1 minute)
- T2 after 10 minutes (± 1 minute)
- T3 after 15 minutes (± 1 minute)
- T4 after 20 minutes (± 1 minute)
- T5 after 25 minutes (± 1 minute)
- T6 after 30 minutes (± 1 minute)
- T7 after 35 minutes (± 1 minute)
- T8 after 40 minutes (± 1 minute)
- T9 after 1 hour (± 5 minutes)
- T10 after 3 hours (± 5 minutes)
- T11 after 6 hours (± 5 minutes)

For each product use, subjective effects of liking, craving, satisfaction, and intention to use will be assessed at the following time points in relation to T0 with a time window as indicated in brackets:

Prior to T_{0M} and T_{0A} (for VAS craving only):

- T-15: within 15 minutes prior to T_0

After T_{0M} and $T_{0A:}$ (for VAS craving, VAS liking "in the moment", and VAS satisfaction "in the moment" assessments):

- T1 after 5 minutes (± 1 minute)
- T2 after 10 minutes (± 1 minute)
- T3 after 15 minutes (± 1 minute)
- T4 after 20 minutes (± 1 minute)
- T5 after 25 minutes (± 1 minute)
- T6 after 30 minutes (± 1 minute)
- T7 after 35 minutes (± 1 minute)
- T8 after 40 minutes (± 1 minute)
- T9 after 1 hour (± 5 minutes)
- T10 after 3 hours (± 5 minutes) (VAS craving and VAS satisfaction only)
- T11 after 6 hours (± 5 minutes) (VAS craving and VAS satisfaction only)

After T_{0M} and $T_{0A:}$ (for VAS liking (overall) assessment)
- T10 after 3 hours (± 5 minutes)

After T_{0M} and $T_{0A:}$ (for VAS intention-to-use again)
- T6 after 30 minutes (± 1 minute)

• T10 after 3 hours (± 5 minutes)

Additional subjective effects will be assessed in the morning and in the afternoon on Day 1 to Day 3 by the PES and the Sensory questionnaire administered at T9, 1 hour (± 5 minutes) after T_{0M} and T_{0A}.

Additional blood samples will be taken for determination of the nicotine concentration to evaluate terminal elimination half-life ($t_{1/2z}$) in relation to T_{0A} on Day 2 at the following time points with a time window as indicated in brackets:
• T1z after 8 hours (± 5 minutes) after T_{0A}
• T2z after 12 hours (± 5 minutes) after T_{0A}

After discharge at Day 3, the subjects will enter a 3-day Safety follow-up period during which AE/SAEs reported by the subjects associated with investigational product (IP) use will be collected and the follow-up of the ongoing AEs/SAEs will be conducted by the study investigational site.

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

3.2 Selection of Study Population

Twenty-four healthy smoking subjects will be randomized to 1 of 6 possible sequences of product use on Day 1 to Day 3 with at least 25% of each sex.

The study population will be stratified by sex. Each sex will have a quota applied to ensure they represent at least 25% of the total randomized subjects.

3.2.1 Inclusion Criteria

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

Inclusion Criteria	Screening	Admission (Day -1)
1. Subject has signed the Informed Consent Form (ICF) and is able to understand the information provided in the ICF.	X	
2. Smoking male or female aged between 21 and 65 years old.	X	
3. Subject has smoked continuously for at least the last 3 years prior to the Screening visit.	X	
4. Subjects has smoked ≥ 10 commercially available cigarettes per day for 4 weeks prior to Screening Visit and Admission. Smoking status will be verified based on a urinary cotinine test (cotinine ≥ 500 ng/mL).	X	X

Inclusion Criteria	Screening	Admission (Day -1)
5. Subject does not plan to quit using tobacco and/or nicotine products within the next 3 months.	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, ECG, and medical history).	X	

3.2.2 Exclusion Criteria

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

Exclusion Criteria	Screening	Admission (Day -3)
1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).	X	
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners).	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), which as per the judgment of the Investigator would jeopardize the safety of the subject.	X	
4. As per the Investigator's judgment, the subject has medical conditions which require or will 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.	X	
5. Subject has donated or received whole blood or blood products within 30 days prior to Screening Visit.	X	

Exclusion Criteria	Screening	Admission (Day -3)
6. Body Mass Index (BMI) < 18.5 kg/m2 or > 32.0 kg/m^2.	X	
7. Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer), which has an impact on CYP2A6 activity		X
8. Subject has a positive serology test for HIV 1/2, Hepatitis B or Hepatitis C.	X	
9. Subject has a history of alcohol abuse, which as per the judgment of the Investigator could interfere with the subject's participation in study.	X	
10. Subject has a positive urine drug including alcohol test.	X	X
11. Subject or one of their family members[a] is a current or former employee of the tobacco industry.	X	
12. Subject or one of their family members[a] is employee of the investigational site or of any other contracted vendors involved in the study.	X	
13. Subject has participated in another clinical study within 30 days prior to the Screening Visit.	X	
14. Subject has been previously screened or enrolled in this study.	X	
15. For women only: subject is pregnant (does not have negative pregnancy test at Screening Visit and at Admission) or is breastfeeding.	X	X
16. For women of childbearing potential only[b]: subject does not agree to use an acceptable method of effective contraception [c].	X	X
17. Use of estrogen-containing hormonal contraception or hormone replacement therapy.	X	X

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

b. Women who are not of childbearing potential meet at least one of the following criteria:
- Have undergone hysterectomy or bilateral tubal ligation,
- Have primary ovarian insufficiency, or

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

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

3.3 Discontinuation of Subjects from the Study

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

Subjects will be informed that they are free to withdraw from the study at any time. Subjects will be questioned for the reason for withdrawal from the study, although they are not obliged to disclose it.

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

When a subject is discontinued or withdraw from the study, all early termination procedures (study protocol Section 9.7) will be performed unless the subject refuses to perform the assessments or the procedures have already been performed during the study day. This information will be fully documented by the Investigator.

Subjects must be discontinued from the study for any of the following reasons:
- Withdrawal of informed consent.
- Any AE/SAE or condition (including clinically significant changes in a laboratory parameter), which at the discretion of the Investigator is not compatible with the subject's continued participation in this study.
- Positive pregnancy test (study protocol Section 8.5).
- If the Sponsor decides to prematurely terminate the study, the subject will be promptly informed by the Investigator. The Investigator should report the fact and the reason in writing to the Independent Ethics Committee (IEC).
- Discontinuation is considered to be in the best interest of the subject, or the other subjects as judged by the Investigator, e.g. SARS-CoV-2 positive.
- Subject is not willing and/or ready to use NP 1.0 after the product test at Admission (Day -1).
- Subject uses any tobacco or nicotine containing product different from the assigned product during confinement.

Subjects may be discontinued from the study for the following reasons:
- Non-compliance to the study procedures based on the judgment of the Investigator.
- Violations of eligibility criteria have been determined (study protocol Section 5.4).

Subjects who will be discontinued from the study before enrolment will be replaced. After enrollment but before randomization, subjects who will be discontinued from the study will

enter the 3-day Safety follow-up period and will be replaced. In general, subjects that are discontinued after randomization will not be replaced.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

PK endpoints, PD endpoints, and amount of nicotine delivered will be analyzed using the PK population.

Safety will be analyzed using the safety population (SAF).

Demographics and baseline characteristics will be summarized in both SAF and PK populations.

4.1.1 Screened Population

The screened population consists of all subjects who underwent screening.

4.1.2 Safety Population (SAF)

The safety population (SAF) is a subset of the screened population and consists of all the subjects who signed ICF consent and have at least one exposure to NP 1.0 (including the product test with NP-1 at Admission).

4.1.3 Pharmacokinetic Population (PK)

The PK Population is a subset of the SAF and consists of all randomized subjects for whom at least one nicotine PK parameter can be derived. Only subjects without major protocol deviations, as defined in Section 4.2.1.1, which have an impact on evaluability of the main objective will be included in the PK population.

4.2 Protocol Deviations

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

4.2.1 Data Collection

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

All deviations will be reviewed to determine their impact when subjects are assigned to analysis populations. Each deviation will be classified as major or minor.

4.2.1.1 Major Protocol Deviations

Subjects with major protocol deviations will be identified (at a population level) to determine whether they will be excluded from the PK population.

Major deviations will include but are not limited to the deviations presented in Table 4.1

Table 4.1 - Definition of Major Protocol Deviation Categories

Sub-Category	Description
Violation	Violation of inclusion/exclusion criteria
Mis-randomization	Violation of the product allocation process, including but not limited to the misclassification of subject's sex at randomization and incorrect product administered according to randomized sequence
Mis-use of product	Use of any nicotine or tobacco–containing product other than the assigned product during the exposure period or use of any nicotine tobacco-containing product during at least 10 hours of abstinence from any nicotine/tobacco containing products (nicotine wash-out). Product use not compliant with planned regimen of single product and 30 minutes product use period
Concomitant medications	Use of any drugs which are known to affect CYP2A6 activity

Among the eligibility criteria, violations of inclusion criteria 1, 2, 3, and 4 or of the exclusion criteria 2 and 14 will be considered as impacting the evaluability or integrity of the primary objective. Other major protocol deviations will be assessed for their impact on the evaluability of the primary objective during the pre-analysis data review meeting.

4.2.1.2 Minor Protocol Deviations

Minor deviations will include, but are not limited to, the deviations presented in Table 4.2.

Table 4.2 - Definition of Minor Protocol Deviation Categories

Sub-Category	Description
Procedural violation	Violation of any study procedures not affecting safety or data evaluability
Time deviation (Plasma nicotine PK sample)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Section 3.1)
Time deviation (other assessment)	Assessments not taken at the correct time or within the allowed time window or date/time is missing (see Section 3.1)
Assessment missing (Plasma nicotine PK sample)	Assessment is missing
Assessment missing (other assessment)	Assessment is missing
Randomized product sequence	Subject randomized not according to the sequence of the subject numbers assigned during the screening visit

4.2.1.3 Assessment Time Points and Assessment Time Windows

Assessment Time Points and Assessment Time Windows presented in Table 4.3.

Table 4.3 – Definition of Collection Time Points and Assessment Time Windows

Assessment	Nominal Time point(s) (relative to T_0)	Time Window
Plasma nicotine PK samples	5 minutes prior to T_0	± 1 minute
	5 minutes after T_0	± 1 minute
	10 minutes after T_0	± 1 minute
	15 minutes after T_0	± 1 minute
	20 minutes after T_0	± 1 minute
	25 minutes after T_0	± 1 minute
	30 minutes after T_0	± 1 minute
	35 minutes after T_0	± 1 minute
	40 minutes after T_0	± 1 minute
	1 hour after T_0	± 5 minutes
	3 hours after T_0	± 5 minutes
	6 hours after T_0	± 5 minutes
VAS craving, VAS liking “in the moment”, VAS satisfaction “in the moment”	within 15 minutes prior to T_0	N/A (VAS craving only)
	5 minutes after T_0	± 1 minute
	10 minutes after T_0	± 1 minute
	15 minutes after T_0	± 1 minute
	20 minutes after T_0	± 1 minute
	25 minutes after T_0	± 1 minute
	30 minutes after T_0	± 1 minute
	35 minutes after T_0	± 1 minute
	40 minutes after T_0	± 1 minute
	1 hour after T_0	± 5 minutes
	3 hours after T_0	± 5 minutes; VAS craving and VAS satisfaction “in the moment” only
	6 hours after T_0	± 5 minutes; VAS craving and VAS satisfaction “in the moment” only
VAS liking (overall) assessment	3 hours after T_{0M} and T_{0A}	± 5 minutes
VAS intention-to-use again	30 minutes after T_0	± 1 minute
	3 hours after T_0	± 5 minutes

Assessment	Nominal Time point(s) (relative to T_0)	Time Window
Product evaluation scale and the Sensory questionnaire	1 hour after T_0	± 5 minutes
Blood samples for λz	8 hours after T_{0A} on Day 2	± 5 minutes
	12 hours after T_{0A} on Day 2	± 5 minutes
ECG	Screening	N/A
	Day -1	N/A
	Day 3	N/A
	Early Termination	N/A
Vital signs	Screening	N/A
	Day -1	N/A
	Days 1, 2, and 3	Before T_{0M}
	Day 3 Discharge	N/A
	Early Termination	N/A

N/A = Not applicable

4.2.2 Data Summarization

Protocol deviations will be summarized in the SAF population by reporting the number and percent of subjects with protocol deviations, and the number of protocol deviations, will be summarized. Summaries will be broken down by main deviation category (major/minor), sub-categories, and evaluability impact. Subjects will be counted once per deviation category and can be counted for more than one deviation category.

4.3 Preliminary Data and Interim Analysis

There will be no interim analysis of this study data.

5. PRODUCT DESCRIPTIONS

The 4 variants of NP 1.0, Velo-NP and Zyn-NP will be provided by the Sponsor. The distribution will be controlled by the Investigator or a qualified and appropriately trained designee.

5.1 Test Products:

The following variants of NP 1.0 will be investigated in this study (Table 5.1).

Table 5.1 Test products

Name	Name in this study	Nicotine per pouch	pH	Moisture	Flavor
NP-1	NP-1	8.4 mg	8.0	30	Cool mint
NP-2	NP-2	8.4 mg	9.0	30	Cool mint
NP-3	NP-3	3.6 mg	8.0	15	Cool mint
NP-4	NP-4	3.6 mg	8.0	30	Cool mint

5.2 Comparator Products:

The following products will be used as the comparators (Table 5.2).

Table 5.2 Comparator products

Name	Name in this study	Nicotine per pouch	Flavor
Velo® Ice Cool	Velo-NP	10 mg	Cool mint
Zyn® Cool Mint Mini Dry	Zyn-NP	3 mg	Cool mint

6. PHARMACOKINETICS

6.1 Collection Schedule for Plasma Nicotine

The blood sample collection schedule for plasma nicotine is described in Table 6.1.

Table 6.1 Plasma Nicotine Samples Collection Schedule

Days 1, 2, and 3 (2 x 12 blood samples on each day)	Prior to start of product use in the morning (T_{0M}) and in the afternoon (T_{0A}): T-1: 5 minutes (± 1 minute) In relation to T_{0M} and T_{0A}: T1 after 5 minutes (± 1 minute), T2 after 10 minutes (± 1 minute), T3 after 15 minutes (± 1 minute), T4 after 20 minutes (± 1 minute), T5 after 25 minutes (± 1 minute), T6 after 30 minutes (± 1 minute), T7 after 35 minutes (± 1 minute), T8 after 40 minutes (± 1 minute), T9 after 1 hour (± 5 minutes), T10 after 3 hours (± 5 minutes), T11 after 6 hours (± 5 minutes).
Day 2 (2 additional blood samples)	Samples for determination of the terminal elimination half-life (t1/2z): In relation to T_{0A} from Day 2: T1z after 8 hours (± 5 minutes) after $T_{0A,}$ T2z after 12 hours (± 5 minutes) after T_{0A}.

6.2 Plasma Nicotine Concentrations

Samples will be analyzed for nicotine in plasma using a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) detection analytical method with the appropriate quality controls in accordance with the Food and Drug Administration (FDA) Guidance for Industry: Bioanalytical Method Validation [1] and in accordance with FDA Good Laboratory Practice regulations (Title 21 CFR Part 58) at [redacted] Bioanalytical Services[redacted].

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

Plasma concentrations as determined at the collection times described in Section 6.1 will be used for the calculation of the plasma nicotine PK parameters.

6.3 Plasma Nicotine Pharmacokinetic Parameters

Nicotine PK parameters will be derived from background-corrected plasma nicotine concentration versus time data using a non-compartmental analysis (NCA) technique using appropriate and validated PK software (e.g., Phoenix WinNonlin version 8.1 or higher).

For nicotine concentrations below the LLOQ (BLQ) for the calculation of descriptive statistics of observed plasma nicotine concentrations:

- BLQ values before T0 will be imputed by LLOQ/2.
- BLQ values after the last quantifiable value are not included in the analysis (e.g., for the calculation of AUC).

- Any BLQ value (after T0 and before the last quantifiable value) would need to be queried* and, if confirmed, it will be imputed by LLOQ/2.

*The query will be triggered by [redacted] data QC, and [redacted] will query the bioanalytical laboratory. The information on the value queried and a summarized response from the bioanalytical laboratory will be part of the SDTM data (e.g. in the CO domain).

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

To minimize the carry-over effect in the nicotine plasma PK parameters due to limited washout periods, the correction for background-concentration (baseline nicotine level obtained pre-use) will be applied to the concentration data. This correction will be implemented by calculating the nicotine exposure parameters using background-corrected concentration values as described below.

The nicotine terminal elimination rate constant λ_z (and $t_{1/2z}$) will be estimated including PK samples listed in Section 6.1 by using a linear regression on the log-transformed plasma nicotine concentration data. The regression analysis should contain data from at least 3 different time points in the terminal phase (including the last quantifiable concentration but excluding the concentration at T_{max}), consistent with the assessment of a straight line on the log-transformed scale. The nicotine plasma background-corrected PK parameters will be derived by performing the NCA on the background corrected concentrations.

For the purposes of background-correction of the plasma concentrations post-baseline the following formula will be applied: $cC_t = C_t - C_0 \cdot * e^{-\lambda z \cdot t'}$. Where, cC_t is the corrected concentration at each time point, C_t is the observed concentration at each time point, C_0 is the pre-use baseline concentration, λ_z is the Day 2 terminal elimination rate constant, t is the actual time since start of product use, and t' is the actual time since the time of the pre-use baseline sample.

In particular, the following PK parameters will be derived from background-corrected nicotine levels following 30 minutes of product use:

C_{max}	Maximum background-corrected plasma concentration. C_{max} will be reported as long as there is at least one quantifiable concentration post T_0.
T_{max}	Time to maximum background-corrected plasma nicotine concentration C_{max}.
$AUC_{0\text{-}5min}$	Area under the background-corrected plasma concentration-time curve from start of product use (T_0) to 5 minutes.
$AUC_{0\text{-}10min}$	Area under the background-corrected concentration-time curve from T0 to 10 minutes.
$AUC_{0\text{-}15min}$	Area under the background-corrected concentration-time curve from T0 to 15 minutes.
$AUC_{0\text{-}20min}$	Area under the background-corrected concentration-time curve from T0 to 20 minutes.

$AUC_{0\text{-}25min}$	Area under the background-corrected concentration-time curve from T0 to 25 minutes.
$AUC_{0\text{-}30min}$	Area under the background-corrected concentration-time curve from T0 to 30 minutes.
$AUC_{0\text{-}35min}$	Area under the background-corrected concentration-time curve from T0 to 35 minutes.
$AUC_{0\text{-}40min}$	Area under the background-corrected concentration-time curve from T0 to 40 minutes.
$AUC_{0\text{-}1h}$	Area under the background-corrected concentration-time curve from T0 to 1 hour.
$AUC_{0\text{-}3h}$	Area under the background-corrected concentration-time curve from T0 to 3 hours.
$AUC_{0\text{-}6h}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 6 hours.
$AUC_{0\text{-}infinity}$	Area under the background-corrected plasma nicotine concentration-time curve extrapolated from T0 to infinity.

All AUC parameters will be calculated using linear trapezoidal with linear interpolation method.

For calculation of λ_z from observed data (to be used for background correction), concentrations BLQ will be set to 0 for pre-administration and prior to the first measurable concentration and set to missing after the last quantifiable concentration (if applicable).

The following steps will apply for the other PK parameters:

- Concentrations BLQ will be set to ½ the LLOQ except for any BLQ values after the last quantifiable concentration which will be set to missing.
- The formula for background correction will be applied.
- After the calculation, pre-product administration values will be assigned a value of zero in the analyses. All other values obtained will be reported as is even if these values are BLQ, except for any negative values, which will be set to zero.

6.4 Pharmacokinetic Data Summarization and Presentation

SAS software (Version 9.4, Cary, North Carolina) will be used for all data presentation and summarization including statistical analyses, summary tables, graphs, and data listings.

Plasma nicotine concentrations (observed and background-corrected), λ_z (observed only), and other PK parameters (background-corrected only) will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data (Missing, n (%)), arithmetic mean (Mean), standard deviation (SD), percent CV (CV%), standard error of the mean (SEM), minimum, first quartile (Q1), median, third quartile (Q3), and maximum.

In addition, geometric mean (Geo. Mean), 95% geometric confidence interval (Geo. 95% CI), and geometric CV (Geo. CV%) will be presented, as applicable.

For observed plasma nicotine concentrations, the number and percent of values below LLOQ (BLQ, n(%)) and above ULOQ (ALQ, n(%)) will be presented in each summary table.

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

For endpoints relating to sampling times (e.g., T_{max}) only n, missing n (%), median, Q1, Q3, minimum and maximum will be presented.

All analyses and summaries will be performed by product and overall. Summaries will be further stratified by sex.

The analytical data will be presented in the tables/listings to the same precision as received from the analytical laboratory.

The level of precision and rounding for the summary statistics will be specified in the TFL shell document.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators. Missing PK data will be treated as missing, and no data imputation will be conducted.

Mean and individual plasma nicotine concentrations will be presented graphically (linear and semi-log plots; linear plots will be presented with and without SD).

6.5 Statistical Analysis of PK Parameters

6.5.1 Main analysis

A mixed model analysis of variance (ANOVA) will be conducted on AUC and C_{max} endpoints in the natural logarithmic scale.

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

A heterogeneous Compound Symmetry matrix will be used to model the variance covariance structure within subjects. If this model fails to converge, then the following variance-covariance matrices will be used (in this order) until one converges: variance Components, Compound Symmetry, and finally without subject's random effect.

The procedure will use the restricted maximum likelihood method and the Kenward-Roger method to compute the degrees of freedom.

The results of this analysis will be presented in terms of geometric least square mean ratios and 95% CI for the 4 respective variants of NP 1.0, Velo-NP, and Zyn-NP ratios. The pairwise comparisons which will be performed are listed in Table 6.2.

Table 6.2 List of pairwise comparisons

	NP-2	NP-3	NP-4	Velo-NP	Zyn-NP
NP-1	X	X	X	X	X
NP-2		X	X	X	X
NP-3			X	X	X
NP-4				X	X

The model described above will be implemented in the SAS® language as:

PROC MIXED data=dataset method=reml;
class Subject Sequence Period Product Sex;
model Log(Parameter) = Sequence Period Product / ddfm=KR;
repeated Product / subject=Subject type=csh;
lsmeans Product / pdiff=LIST_OF_PAIRWISE_COMPARISONS cl;
RUN;

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

6.5.2 Sensitivity Analysis

In cases where the plasma concentrations cannot be background-corrected in two or more subjects in a sequence, a sensitivity analysis will be performed similarly to the main analysis, whereby:

- If the subject's terminal elimination rate cannot be estimated it will be substituted by the average terminal elimination rate of the subjects having the same sex,
- If the uncorrected nicotine concentration at baseline is not available for the period 2 or 3, it will be substituted by the extrapolation of the previous concentrations using the terminal elimination rate.

6.5.3 Supplementary Analysis

In case of any uncorrected nicotine concentration at T_0 [uC_0] greater than 25% of their uncorrected maximum value, a supplementary analysis of the endpoints will be performed similarly to the main analysis, whereby data of these subjects for this specific product use period will be excluded from the analysis.

7. PHARMACODYNAMIC EFFECTS (SUBJECTIVE EFFECTS AND RELATED BEHAVIORAL ASSESSMENTS)

7.1 Data Collection

7.1.1 Product Evaluation Scale

Product evaluation will be assessed via a subject self-reported outcome measure, the Product Evaluation Scale (PES) [2, 3].

This 21 items measure consists of 4 multi-item scales and 3 single-item scales, arising from an adaptation of the modified cigarette evaluation questionnaire (mCEQ) [2] to conform to rating oral tobacco products [3].

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

- Product satisfaction (satisfying, tastes good, enjoy the product, enjoy the sensations in month), average of the item scores from questions 1, 2, 3, and 12.
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger), average of the item scores from questions 4, 5, 6, 7, and 8.
- Aversion (dizziness, nausea, too much nicotine, bothersome side effects), average of the item scores from questions 9, 10, 16, and 18.
- Relief (relief craving, relief withdrawal symptoms, relief urge to smoke, enough nicotine, craving for a cigarette), average of the item scores from questions 11, 13, 14, 15, and 20.
- Easy to use (single-item assessment), item score from question 17.
- Comfortable using (single-item assessment), item score from question 19.
- Concerned about dependence (single-item assessment), item score from question 21.

Subjects will be asked to assess the items of the questionnaire on a 7-point scale, ranging from 1 = “not at all” to 7 = “extremely”. Only item 20 is reversed (1 = “extremely”, and 7 = “not at all”).

For the purpose of this study, the comfortable using in public single-item was reworded to a hypothetical situation, given subjects will not use the product in public in this specific study setting.

Each PES subscale will be treated as a continuous variable. For each multi-item subscale, the score 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 as missing. Higher scores indicate greater intensity on that scale.

On Day 1 to Day 3, PES will be collected at 1 hour ± 5 minutes after T_{0M} and T_{0A},

7.1.2 VAS Craving Assessment

Cigarette craving will be assessed using a one-item self-reported craving VAS [4], asking subjects to rate craving for cigarettes (*How strong is your craving for cigarettes?),* on a 100 mm unipolar scale, ranging from 0 (no craving) to 100 (strong craving).

On Day 1 to Day 3, VAS craving assessment will be collected at: Within 15 minutes prior to T_0, after T_0 at 5 minutes ± 1 minute, 10 minutes ± 1 minute, 15 minutes ± 1 minute, 20 minutes ± 1 minute, 25 minutes ± 1 minute, 30 minutes ± 1 minute, 35 minutes ± 1 minute, 40 minutes ± 1 minute, 1 hour ± 5 minutes, 3 hours ± 5 minutes, 6 hours ± 5 minutes.

In addition, VAS-craving assessment averaged during the sequence’s period (from T1 to T11) will also be calculated for each subject at each product use period and summarized using descriptive statistics, as those variables will be used as a covariate for the inferential

analysis for objective 4. The AUCs for to T1 to T11 will be computed and added to the descriptive statistics.

7.1.3 VAS Liking Assessment

Liking will be assessed using a one-item self-reported liking VAS, asking subjects to rate liking for product *(At this moment, my liking for this product is:)* on a 100 mm bipolar scale, ranging from 0 (strong disliking) to 100 (strong liking), with a neutral middle point, as recommended in the FDA guidance for industry on abuse liability assessment [5].

Similarly, overall liking will be assessed using a one-item self-reported liking VAS *(Overall, my liking for this product is:)* on a 100 mm bipolar scale, ranging from 0 (strong disliking) to 100 (strong liking), with a neutral middle point.

On Day 1 to Day 3, VAS liking assessment will be collected at: After T_0 at 5 minutes ± 1 minute, 10 minutes ± 1 minute, 15 minutes ± 1 minute, 20 minutes ± 1 minute, 25 minutes ± 1 minute, 30 minutes ± 1 minute, 35 minutes ± 1 minute, 40 minutes ± 1 minute, 1 hour ± 5 minutes, 3 hours ± 5 minutes, 6 hours ± 5 minutes.

In addition, VAS-liking assessment averaged over the product use period (from T1 to T6) and during the sequence period (T1 to T9) will also be calculated for each subject at each product use period and summarized using descriptive statistics as those variables will be used as a covariate for the inferential analysis for objective 4. The AUCs for to T1 to T11 will be computed and added to the descriptive statistics.

Similarly, overall liking will be assessed using a one-item self-reported liking VAS *(Overall, my liking for this product is:)* on a 100 mm bipolar scale, ranging from 0 (strong disliking) to 100 (strong liking), with a neutral middle point.

On Day 1 to Day 3, VAS overall liking assessment will be collected at 3 hours ± 5 minutes after T_{0M} and T_{0A}.

7.1.4 VAS Satisfaction

Satisfaction will be assessed using a one item self-reported satisfaction VAS, asking subjects to rate product satisfaction *(Is the product 'satisfying' right now?)* on a 100 mm unipolar scale, ranging from 0 (not at all) to 100 (extremely), as recommended by Vansickel [6] to meet current regulatory recommendations in human abuse liability of tobacco and nicotine products.

On Day 1 to Day 3, VAS satisfaction will be collected at: After T_0 at 5 minutes ± 1 minute, 10 minutes ± 1 minute, 15 minutes ± 1 minute, 20 minutes ± 1 minute, 25 minutes ± 1 minute, 30 minutes ± 1 minute, 35 minutes ± 1 minute, 40 minutes ± 1 minute, 1 hour ± 5 minutes, 3 hours ± 5 minutes, 6 hours ± 5 minutes.

In addition, VAS product satisfaction assessment during the sequence's period (from T1 to T11) will also be calculated for each subject at each product use period and summarized using descriptive statistics as those variables will be used as a covariate for the inferential analysis for objective 4. The AUCs for to T1 to T11 will be computed and added to the descriptive statistics.

7.1.5 VAS Intention to Use Again

Intention to use again will be assessed using a one-item self-reported VAS, asking subjects to rate intention to use product again *(How likely are you to use this product again)* on a 100 mm bipolar scale, ranging from 0 (very unlikely) to 100 (very likely), with a neutral middle point.

On Day 1 to Day 3, VAS satisfaction will be collected at 30 minutes ± 1 minute, and 3 hours ± 5 minutes after T_{0M} and T_{0A}.

7.1.6 Sensory questionnaire

Sensory experience will be assessed with the sensory questionnaire which consists of 9 single items (strength of sensation in mouth, strength of sensation in throat, tingling sensation in gums, enjoyment of tingling sensation in gums, experience of dripping from the pouch, satisfaction with dripping, satisfaction with product duration, comfort with pouch size, and comfort with pouch against the gums) assessed on a 7-point scale, ranging from 1 = "not at all" to 7 = "extremely".

Each item will be analyzed individually, no total score will be computed on the Sensory questionnaire.

This questionnaire was developed internally by PMP S.A. based on consumer qualitative insights conducted with users of nicotine pouches in PMP S.A. consumer research studies.

On Day 1 to Day 3, the Sensory questionnaire will be conducted at 1 hour ± 5 minutes after T_{0M} and T_{0A},

7.2 Data Summarization

Descriptive statistics (n, mean, SD, CV%, SEM, minimum, Q1, median, Q3, maximum, and 95% CI of mean) of the PES questionnaire including the subscale scores, VAS craving assessment, VAS liking assessment, VAS overall liking assessment, VAS satisfaction, VAS intent-to-use again, and sensory questionnaire will be provided by study product and assessment time point, when applicable. Change from baseline (pre-product use) for VAS craving score will be summarized by study product and assessment time point. Individual responses will be listed. AUCs for from T1 to T11 for VAS craving assessment, VAS liking assessment and VAS satisfaction assessment will be computed and displayed in summary tables. Summaries will be further stratified by sex.

7.3 Inferential Analysis

An analysis of covariance (ANCOVA) will be conducted by product use. The PK parameters (C_{max}, T_{max}, $AUC_{infinity}$, as applicable) will be transformed (except for the T_{max}) in the natural logarithmic scale. The model will include terms for sequence, period and the PD parameters mentioned in the Objective 4. The effect of VAS score will be analyzed in different models with:

- VAS-liking "in the moment" averaged over the product use period (from T1 to T6)
- VAS-liking "in the moment" averaged during the sequence period (T1 to T9)

- VAS product satisfaction "in the moment" during the sequence's period (from T1 to T11)
- VAS-craving averaged during the sequence's period (from T1 to T11)
- PES
- Sensory questionnaire

The results of this analysis will be presented by product in terms of:

- The percentage of variance explained by the PD parameter
- The standardized effect of the PD parameter, defined as the mean effect divided by the square root of its variance.

The ANCOVA analysis will be performed using the following SAS code:

PROC MIXED data=< > method=type3;

By product;

class sequence period;

model log(PK parameter) = sequence period score/ddfm=KR solution;

run;

A multivariate analysis to analyze the marginal effect of nicotine concentration, pH and moisture of NP 1.0 products will be performed. This analysis will be done using only NP 1.0 data. The PK parameters will be transformed in the natural logarithmic scale. The model will include covariates encoded as low and high for nicotine concentration (3.6 mg = LOW and 8.4 mg = HIGH), PH level (8.0 = LOW and 9.0 = HIGH) and moisture percentage (15% = LOW and 30% = HIGH).

The results of this analysis will be presented by product in terms of:

- The percentage of variance explained by the covariates (nicotine concentration, pH level and moisture)
- The standardized effect of the covariates (nicotine concentration, pH level and moisture) defined as the mean effect divided by the square root of its variance.

The multivariate analysis will be performed using the following SAS code:

PROC MIXED data=< > method=type3;
By product;
Class Nicotine_concentration PH Moisture
model log(PK parameter) = Nicotine_concentration PH Moisture/ddfm=KR solution;
run;

Another ANCOVA will be conducted similarly to the above with the exception that it will be performed overall using mixed effects ANCOVA where the model will include, in addition, the subject as a categorical random effect to model the within subject correlations.

The ANCOVA analysis will be performed using the following SAS code:

```
PROC MIXED data=< > method=type3;
By product sex;
class subject sequence period;
model log(PK parameter) = sequence period score/ddfm=KR solution;
random subject;
run;
```

8. SAFETY

All CRF data will be listed by subject and chronologically by assessment time points. This will include rechecks, unscheduled assessments, and early termination.

Applicable continuous variables will be summarized using number of subjects (n), number and percent of subjects with missing data, arithmetic mean, standard deviation (SD), minimum, median, and maximum.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n and percentage will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

Screen failure subjects will be listed.

8.1 Disposition of Subjects

Subjects will be summarized by number of subjects screened, enrolled, exposed to NP 1.0, randomized, completed, and discontinued the study with discontinuation reasons. Individual subject product use status (i.e., which products were administered to each subject) will also be provided along with their study completion status and date of study completion or discontinuation. The number of subjects administrated for each study product will also be presented.

8.2 Demographics

Descriptive statistics will be calculated overall for continuous variables (age, weight, height, and body mass index [BMI]) and further stratified by sex.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) overall and further stratified by sex.

Demographics will be summarized for the SAF and PK population.

8.3 Tobacco/Nicotine-Containing Product Use History Questionnaire

At the Screening Visit, subjects will be asked questions about their tobacco-and/or nicotine-containing products use history. The questions will capture frequency and quantity of tobacco and/or nicotine-containing product use over the past 4 weeks, number of continuous years of cigarette smoking, and intention to quit using tobacco and/or nicotine products within the next 3 months.

Descriptive statistics will be calculated for continuous variables overall and further stratified by sex. Frequency counts will be provided for categorical variables overall and further stratified by sex. The analysis will be for the SAF and PK population.

8.4 Fagerström Test for Nicotine Dependence (FTND)

Level of nicotine dependence will be assessed using the FTND in its revised version [7] as updated in 2012 [8].

The questionnaire consists of six questions. The scores obtained on the test permit the classification of nicotine dependence into three levels: Mild (0 to 3 points); Moderate (4 to 6 points); Severe (7-10 points) [8].

Descriptive statistics (including number of subjects (n), number and percent of subjects with missing data, median, first and third quartiles, and minimum and maximum) will be calculated for FTND score overall and further stratified by sex. In addition, frequency counts will be provided for nicotine dependence levels (mild, moderate, and severe) and further stratified by sex. The analysis will be for the SAF and PK population.

8.5 Medical History

All Medical Histories and Concomitant Diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), using the version specified in the DMP and listed by subject.

8.6 Adverse Events

All AEs occurring during this clinical trial will be coded using MedDRA® using the version specified in the DMP.

All AEs captured in the database will be listed in by subject data listings including verbatim term, coded term, product, severity, relationship to study product, and action taken; All adverse events will be summarized. Adverse events that occur after ICF and prior to the product test on Day -1 and those that occur during the safety follow up (FU) period (after discharge to safety FU visit) will be summarized separately under admission/safety FU period.

A study product use-emergent adverse event is defined as an AE that is starting or worsening at the time of or after study product administration. An AE that occurs during the washout period between study products is considered study product use emergent to the last study product given.

If the onset time of an AE is missing and the onset date is the same as the product administration date, the AE will be considered product use-emergent to the prior and current product. If the onset time of an AE is missing and the onset date does not fall on a product administration date, the AE will be considered product use-emergent for the last product administered. If the onset date of an AE is missing, the AE will be considered product use-emergent and attributed to each product on the study, unless the onset date is known to have occurred within or between specific product periods.

All PUEAEs will be summarized by product and overall. The number and percentage of subjects with AEs, SAEs (including deaths), and product events listed will be tabulated by

system organ class and preferred term. Summaries will also be presented for AEs leading to product discontinuation, AEs leading to study discontinuation, AEs by relatedness to product exposure (including expectedness) and relatedness to study procedures, AEs by severity, and AE by action taken related to the product. Tabulations will be performed for both the number of subjects experiencing an event and the number of events.

SAEs, if present, will also be listed. Applicable narratives will be included in the CSR.

8.7 Clinical Laboratory Tests (Clinical Chemistry, Hematology, Urinalysis)

Clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) will be performed at Screening, Admission (Day -1), and at Discharge (Day 3), or an early termination assessment will be performed, as applicable.

Out-of-range values and corresponding recheck results will be listed. Other lab results within this panel and time point will also be listed.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by study day. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected on Admission (Day -1). Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

8.8 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, and respiratory rate) will be measured at Screening, Admission (Day -1), Day 1 to Day 3 prior to T_{0M}. If applicable, an early termination assessment will be performed.

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

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

Descriptive statistics will be reported for vital signs measurements (blood pressure, pulse, respiratory rate) by study day. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected prior to T_{0M} on Day 1. Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries.

8.9 Electrocardiogram

An ECG will be recorded at Screening, Admission (Day -1), and at Day 3. If applicable, an early termination assessment will be performed.

The ECG testing will be performed as per the investigational site standard practice. A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval, corrected by the ECG device according to Fridericia's formula [QTcF]. Every ECG has to be assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant.

Descriptive statistics will be presented for each ECG parameter by study day. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to the first product administration, which may include unscheduled or recheck results. This will typically be the result collected at Admission (Day -1). Post product use unscheduled events or rechecks will not be included in summaries. Similarly, early termination results will not be included in summaries. QTcF values that are > 450 msec or increase from baseline > 30 msec will be flagged in the data listing.

8.10 Prior and Concomitant Medications

All prior and concomitant medications will be listed by subject. Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization Drug Dictionary) using the version defined in the DMP. Concomitant procedures recorded during the study will be listed by subject. Concomitant medications will be summarized using frequency count by product.

8.11 Physical Examination

A physical examination will be conducted at Screening, Admission (Day -1) and at the Day of Discharge (Day 3). If applicable, an early termination assessment will be performed.

All data found in the CRF will be listed. Physical examination has to be assessed as normal, abnormal – clinically not significant, or abnormal – clinically significant. Change in physical examination from baseline will be discussed in the CSR.

8.12 Spirometry

Spirometry without bronchodilator will be performed at the Screening visit in accordance with the 2019 guideline of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Joint Task Force on the standardization of spirometry (Graham, B.L., et al., 2019). Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set.

Every Spirometry has to be assessed as normal, abnormal – clinically not significant, or abnormal – clinically significant.

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

Assessed parameters will include: Forced expiratory volume in 1 second (FEV1), FEV1 % predicted, Forced vital capacity (FVC), FVC % predicted, and FEV1/FVC.

Spirometry parameters will be listed by subject and summarized using descriptive statistics.

8.13 Cytochrome P450 2A6 (CYP2A6) Activity

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

On Day -1, one blood sample will be collected for determination of CYP2A6 activity (cotinine and trans-3'-hydroxy-cotinine) prior to the NP 1.0 product test.

Individual results will be listed and descriptive statistics will be presented for the SAF and PK population.

9. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

In section 7.2 AUCs related to T1 to T11 for VAS craving assessment, VAS liking assessment and VAS satisfaction assessment have been added to the descriptive statistics.

In section 8.12, it is specified that the investigator will define ranges to determine normal or abnormal Spirometry results.

All other analyses described in this SAP are aligned with those analyses described in the protocol.

10. REFERENCES

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