PHILIP MORRIS PRODUCTS S.A.

Clinical Study Protocol

Study Number:	P5-PK-01-EXP
Study Title:	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
Short title:	Nicotine pharmacokinetics and subjective effects of Nicotine pouch 1.0 nicotine pouches compared to Velo® Ice Cool and Zyn® Cool Mint Mini Dry in healthy smokers
Product Name:	Nicotine pouch 1.0
Sponsor:	Philip Morris Products S.A. Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	2.0, Approved
Date:	07 Mar 2022
Authors:	[redacted], PhD, Clinical Scientist [redacted], PhD, Biostatistician [redacted], MD, Medical Safety Officer

VERSION HISTORY

Version	Date	Protocol Update/Amendment
2.0	07 Mar 2022	Amendment 1
Original Document 1.0	04 Feb 2022	Not applicable

SUMMARY OF CHANGES FROM PREVIOUS VERSION

- Appendix B: Safety laboratory amended

SYNOPSIS

Sponsor:

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

Name of Product:

Nicotine pouch 1.0

Study Title:

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

Study Number:

P5-PK-01-EXP

Short Title:

Nicotine pharmacokinetics and subjective effects of Nicotine pouch 1.0 nicotine pouches compared to Velo® Ice Cool and Zyn® Cool Mint Mini Dry in healthy smokers

Exploratory Objective and Endpoints:

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

Endpoints (Day 1 to Day 3):

- 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 timepoints 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 Nicotine pouch 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 sale (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 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}]
- Score of overall product liking by the VAS-liking 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}, VAS-S_{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 Product Evaluation Scale 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 Nicotine pouch 1, Velo-NP and Zyn-NP. Reporting of this objective will be separate from the main Clinical Study Report.

Endpoint (Day 1 to Day 3)

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

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 Nicotine pouch 1.0 compared to marketed Velo-NP and Zyn-NP. In addition, PD effects will be evaluated to provide further insights on Nicotine pouch 1.0 product acceptance and abuse liability. The study will be conducted with 3 periods and 6 sequences in a Williams design (cross-over). The assessments to be performed will be as described in the schedule of events (Appendix A). The overall design will be as follows:

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.

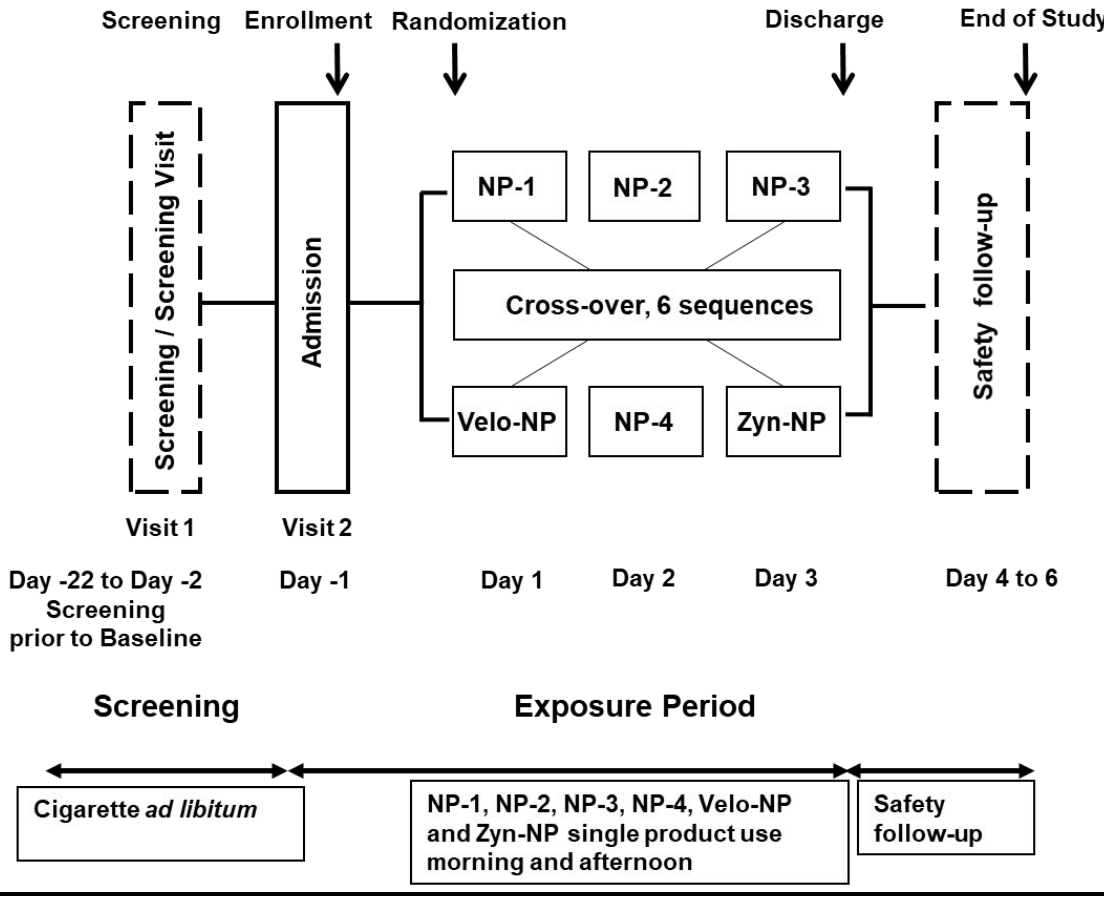

Figure 1 Study Design

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.

At 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 Nicotine pouch 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 Nicotine pouch 1.0, Velo-NP and Zyn-NP during the study after product test will start their exposure period of 3 days.

Twenty-four 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.

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 nicotine pouch (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 T0 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 Product Evaluation Scale (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 IP use will be collected and the follow-up of the ongoing AEs/SAEs will be conducted by the study investigational site.

Study Population and Main Criteria for Inclusion/Exclusion:

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

1. Subject has signed the ICF and is able to understand the information provided in the ICF.
2. Smoking male or female aged between 21 and 65 years inclusive.
3. Subject has smoked continuously for at least the last 3 years prior to the Screening visit.
4. Subject 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).
5. Subject does not plan to quit using tobacco and/or nicotine products within the next 3 months.
6. Smoking, healthy subject as judged by the Investigator or designee based on available assessments from the Screening period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG and medical history).

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

1. As per the Investigator's judgment, the subject cannot participate in the study for any reason other than medical (e.g., psychological, social reason).
2. Subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners).
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.
4. As per the Investigator's judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization), which may interfere with the study participation and/or study results.
5. Subject has donated or received whole blood or blood products within 30 days prior to Screening Visit.
6. BMI < 18.5 kg/m2 or > 32.0 kg/m^2.
7. Subject has received medication within 14 days or within 5 half-lives of the drug prior to Admission (whichever is longer), which has an impact on CYP2A6 activity.
8. Subject has a positive serology test for HIV 1/2, Hepatitis B or Hepatitis C.
9. Subject has a history of alcohol abuse, which as per the judgment of the Investigator could interfere with the subject's participation in study.
10. Subject has a positive urine drug including alcohol test.
11. Subject or one of their family members [a] is a current or former employee of the tobacco industry.

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.
13. Subject has participated in another clinical study within 30 days prior to the Screening Visit.
14. Subject has been previously screened or enrolled in this study.
15. For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding.
16. For women of childbearing potential only [b]: subject does not agree to use an acceptable method of effective contraception [c].
17. Use of estrogen-containing hormonal contraception or hormone replacement therapy.

a. As defined by US Food and Drug Administration (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.

Investigational Products; Dose; and Mode of Administration:

The 4 variants of Nicotine pouch 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.

The following variants of NP 1.0, Velo-NP and Zyn-NP will be investigated:

Test Product

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

Comparator Product

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

Duration of Study:

The entire study per subject will between 8 and 27 days. This will include a screening period of up to 21 days prior to Admission (Day -22 to Day -2), 3 days of confinement (after enrollment on Day -1 to discharge on Day 3, (3 overnight stays), and a 3-day Safety follow-up period (from time of Discharge at Day 4 to Day 6). The end of the study (EOS) for a subject is defined as the end of the Safety follow-up period. The end of the whole study corresponds to the individual EOS of the last subject.

Statistical Methods:

Demographics and baseline characteristics will be summarized for the safety population and PK populations.

PK, PD, and extent of use parameters will be summarized in the PK population, by product and for all the planned timepoints.

Nicotine PK parameters will be derived from Background-Corrected Plasma Nicotine Concentrations using NCA.

Safety data will be listed and tabulated in the Safety population. Safety variables collected during exposure period will also be reported by sequence. All data will be presented in listings, ordered by randomized sequence, subject, and time point unless otherwise specified.

All endpoints will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data, arithmetic means, and standard deviations (mean and SD), median, first and third quartiles, minimum and maximum, and change from baseline.

For log normally distributed endpoints, geometric mean, geometric CV, confidence interval of the geometric mean, and percent change from baseline will be presented in addition.

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

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

A mixed model analysis of variance (ANOVA) will be conducted on C_{max}, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}10min}$, $AUC_{0\text{-}15min}$, $AUC_{0\text{-}20min}$, $AUC_{0\text{-}25min}$, $AUC_{0\text{-}30min}$, $AUC_{0\text{-}35min}$, $AUC_{0\text{-}40min}$, $AUC_{0\text{-}1h}$, $AUC_{0\text{-}3h}$, $AUC_{0\text{-}6h}$, and $AUC_{0\text{-}infinity}$ endpoints in the natural logarithmic scale. The results of this analysis will be presented in terms of geometric least square mean ratios and 95% confidence intervals (95% CI).

The analysis of T_{max} will be conducted using non-parametric tests and Hodges-Lehmann estimates of median difference with its derived 95% CI.

Sample Size and Evaluation:

The sample size is empirically based as there are no considerations for statistical hypothesis. A total of 24 subjects is expected to be sufficient to obtain a precision smaller than 15% if the NP-1: Velo-NP C_{max} ratio is 1 and the within correlation is 0.7.

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
$AUC_{0\text{-}2min}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 2 minutes after T_0
$AUC_{0\text{-}4min}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 4 minutes after T_0
$AUC_{0\text{-}Tmax}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to subject-specific time to maximum plasma concentration after T_0
$AUC_{0\text{-}10hours}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to 10 hours after T_0
$AUC_{0\text{-}last}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 to time of last quantifiable concentration
$AUC_{0\text{-}infinity}$	Area under the background-corrected plasma nicotine concentration-time curve from T_0 extrapolated to infinity
BMI	Body mass index
CDC	Centers for disease control and prevention
C_{max}	Background-corrected maximum concentration
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTMS	Clinical trial management system
CV (documentation)	Curriculum vitae
CV (statistics)	Coefficient of variation
CYP2A6	Cytochrome P450 2A6
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study

FDA	US Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTND	Fagerström test for nicotine dependence (revised version)
FVC	Forced vital capacity
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HPHCs	Harmful and potentially harmful constituents
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of the normal range
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
NCA	Non-compartmental analysis
PES	Product evaluation scale
PD	Pharmacodynamics
PK	Pharmacokinetics
PMP S.A.	Philip Morris Products S.A.
QC	Quality control
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SHM	Sample handling manual
SOP	Standard operating procedure
T	Time point
T0	Time point of the start of product use

t½	Half-life
t½z	Terminal elimination half-life
Tmax	Time to background-corrected maximum plasma nicotine concentration
uC	uncorrected nicotine concentration (at T0: uC0)
ULN	Upper limit of the normal range
ULOQ	Upper limit of quantification
VAS	Visual Analog Scale
WHO	World Health Organization

EXPLANATION OF TERMS

The following special terms are used in this protocol:

Alternates	Subjects who signed the ICF, met the inclusion and exclusion criteria, were enrolled but are not randomized due to a sufficient number of subjects are already randomized. Alternates will be discontinued from the study prior to randomization and will enter the 3-day Safety follow-up period.
End of Study	The end of the study (EOS) for a subject is defined as the end of the Safety follow-up period. The end of the whole study corresponds to the individual EOS of the last subject.
Cigarette	The term 'cigarette' refers to manufactured and commercially available regular or menthol cigarettes and excludes hand-rolled cigarettes, cigars, pipes, bidis, and other nicotine-containing products.
Enrollment	At Admission (Day -1) for eligible subjects after all applicable inclusion and exclusion criteria have been satisfactorily assessed and met.
Randomization	Assignment to the respective sequence of Nicotine pouch 1.0, Velo-NP and Zyn-NP use at Admission (Day -1).
Screen failure	Subject who signs the ICF but is not enrolled at Admission (Day -1).

1 ETHICS AND REGULATIONS

1.1 Independent Ethics Committee (IEC)/Independent Review Board (IRB) Approval

Prior to the start of the study, the clinical study protocol, together with its associated documents (informed consent form [ICF] including the subject information sheet, subject recruitment procedures [e.g., advertisements], written information to be provided to the subjects, Investigator's brochure [IB], available safety information, curriculum vitae of the Investigator(s) and designee(s) and/or other evidence of qualifications and any other documents requested by an Independent Ethics Committee (IEC)/Institutional Review Board [IRB]), will be submitted for review and approval to the relevant IEC/IRB according to the appropriate provisions. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance for Good Clinical Practice (GCP) [1] and local requirements, as applicable.

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

The written approval from the IEC/IRB will be filed in the Investigator file, and a copy will be filed in the study master file at the Sponsor or designated organization. The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB.

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

These requirements for approval should in no way prevent any action from being taken by the Investigator(s) or by the Sponsor in order to eliminate immediate hazards to the subjects. If such a change to the protocol is felt to be necessary by the Investigator(s), and is implemented for safety reasons, the Sponsor and the IEC/IRB should be informed immediately. The Investigator(s) is(are) responsible for local reporting (e.g., to the IEC/IRB) of serious adverse events (SAEs) that occur during the study, according to local regulations.

Relevant safety information will be submitted to the IEC/IRB during the study in accordance with national regulations and requirements. Medically qualified study personnel will be available during the study.

1.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [2] and are consistent with the principles of ICH/GCP [1].

The Investigator(s) or designee(s) agree(s) to conduct the clinical study in compliance with the protocol agreed with the Sponsor and approved by the IEC/IRB. The Investigator(s) and the Sponsor must sign the protocol (and protocol amendments, if applicable) to confirm this agreement. A copy of the Declaration of Helsinki is located in the Investigator's study file.

1.3 Subject Information and Consent

1.3.1 Informed Consent Form for Study Participation

Before or at Screening, the Investigator or designee will ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study, and the Investigator or the designee will answer all questions the subject might have to his/her full satisfaction. The subject will have sufficient time for consideration of his/her participation in the study and will be notified that he/she is free to discontinue his/her participation at any time.

Once the subject has received all the necessary information, and if he/she agrees to participate, this will be documented in the ICF by the date and signature of both the subject and the Investigator or designee who conducted the informed consent discussion during Screening Visit. Any procedures specifically described in and related to the study protocol and study conduct, will not be performed before the ICF has been signed. The exact date and time of ICF signature will be captured in the volunteers' registration log.

The personally signed and dated original ICF(s) must be kept by the Investigator and filed in the Investigator study file at the site or with the subject's files and a copy must be given to the subject. The subject will be informed that if he/she withdraws from the study, the data collected until the point of withdrawal will be maintained as part of the study data and the samples collected prior to withdrawal will be analyzed, unless he/she refuses in writing. The subject will be informed that additional data analysis not mentioned in the protocol or in the statistical analysis plan (SAP) may be performed with the collected data at a later time. Any additional analysis performed will be covered by data confidentiality, as for the main analysis described in this protocol.

1.3.2 Amendment to the Informed Consent Form

If a protocol amendment is required, or if any new information regarding the risk profile of the investigational product (IP) becomes available for any other reason deemed necessary, an amendment to the ICF may be required. If a revision of the ICF is necessary, the Investigator(s) or designee will, with the support of the Sponsor, ensure that the documents

have been reviewed and approved by a responsible IEC/IRB before subjects are required to re-sign the ICF (including date and time). If new and important safety information is received, subjects who already completed or have been discontinued from the study will be informed by letters, emails or phone calls.

1.4 Good Clinical Practice and Regulatory Requirements

The procedures set out in this clinical study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator and designee abide by the principles of the ICH GCP Guideline [1]. These guidelines apply specifically to pharmaceutical development, but nevertheless provide a robust and ethical framework for conducting a clinical study with products such as Nicotine pouch 1.0. The study will also be conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki [2].

In addition, the Investigator or designee will carry out the clinical study in accordance with applicable national and local laws of the pertinent regulatory authorities.

2 INTRODUCTION

2.1 Background

2.1.1 Smoking-Related Diseases and Harm Reduction Strategy

Cigarette smoking causes pulmonary, cardiovascular and other serious diseases in smokers [3]. There is no safe cigarette, and the best way for smokers to reduce the adverse health consequences of smoking is to quit. Despite the risks which are attributable to smoking, some smokers decide to continue smoking. The development of novel tobacco and nicotine containing products with the potential to be less harmful than cigarettes represents an approach to reduce cigarette-related deaths and diseases among smokers who would have otherwise continued smoking [4]. Philip Morris Products S.A. (PMP S.A.) is developing such alternative products that have the potential to reduce individual risk and population harm in comparison to smoking cigarettes. These products aim to substantially reduce or eliminate the exposure to harmful and potentially harmful constituents (HPHCs) generated from cigarette smoke, with the exception of nicotine, while providing an acceptable substitute for cigarettes.

The Tobacco Advisory Group of the Royal College of Physicians (RCP) suggested in 2007 that "if nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives could be saved" [5]. In a report published in 2016 [5], the Tobacco Advisory Group of the RCP propounded further that "if nicotine could be delivered effectively and acceptably to smokers without smoke, most if not all of the harm of smoking could probably be avoided". Tobacco health advocates and regulators are increasingly embracing this concept [6-10].

PMP S.A. is developing a portfolio of smoke-free, nicotine-containing, products that replicate the sensorial and taste attributes of cigarettes as much as possible, while delivering nicotine in a manner that is significantly less harmful than cigarette smoke. As part of this portfolio, PMP S.A. has developed nicotine pouches.

Nicotine Pouch 1.0 (NP 1.0) is a nicotine-containing, tobacco-free, oral product. NP 1.0 is pre-portioned and intended for uptake of the nicotine via the oral mucosa. In addition to nicotine, NP 1.0 contains among other ingredients flavorings, sweeteners, and pH buffering agents. The ingredients are [redacted] enclosed in a pouch. The nicotine is of pharmaceutical grade, all other powder ingredients are of food grade and the pouch material (fleece) is of food contact grade. NP 1.0 is placed between the lip and the gums. Nicotine transfers through the gum epithelium. The nicotine and flavors are released during a product use period of 20-40 mins. Product use ends by removing the pouch from the mouth. The used nicotine pouch can be discarded.

2.1.2 Description of the Product and Scientific Findings

Tobacco-free nicotine pouches (NP) are similar in appearance to an established form of smokeless tobacco product commonly used in Scandinavia called 'snus'. Swedish-style snus is a type of pouched smokeless tobacco that does not produce excessive salivation. Like Swedish snus, NP are placed between the upper lip and gum but differ in that there is no leaf tobacco in them [11]. The user inserts the pouch NP between the upper lip and gum, leaves it there while the nicotine and flavor are released typically during a period of 20-40 mins. NP 1.0 is similar in appearance and use to Swedish-style snus, another oral smokeless tobacco product traditionally used in Sweden since the 1800s. NP 1.0 is manufactured without tobacco and therefore TSNAs may further reduce the risk to consumers compared to the use of Swedish snus.

NP were introduced for marketing in 2016 in the United States (US), 2017 in Scandinavia and 2018 in the United Kingdom (UK) [12].

The NP 1.0 is designed to deliver nicotine orally, through oro-mucosal absorption at the gums of the user. It has the following main components:

- A wet nicotine containing powder
- A pouch containing 560mg of powder
- A plastic can containing 20 to 24 bags.

[redacted]

For details on composition of NP 1.0 see Investigator's Brochure.

Weight of the [redacted] powder in each NP 1.0 pouch is approximately 560 mg per NP. All [redacted] powder ingredients are food grade.

NP 1.0 has not been tested in humans or marketed yet. Various other products with similar compositions are currently marketed, e.g. Velo® Ice Cool, Zyn® Cool Mint Mini Dry. Nicotine pouches were first described in clinical studies as a new formulation for nicotine replacement treatment [13].

Various factors affect the absorption of nicotine from NP, including pH levels, nicotine content, and duration of product use. Other factors such as pouch surface area, saliva penetration, and product use characteristics are also relevant while flavor has been described not to influence the nicotine uptake [14]. While a direct correlation is suggested between the duration of product use and nicotine absorption, a correlation between the amount of nicotine per pouch did not correlate directly with the amount of nicotine absorbed [15].

Nicotine extraction from various NP has been described to range between approximately 45% to 60% [16, 17]. NP usually have a longer time to reach maximum nicotine concentration (T_{max}) and a lower maximum nicotine concentration (C_{max}) and lower positive subjective effects compared to subjects' own cigarettes [14]. Thus, it is likely that NP results in lower reinforcing effects and abuse potential than cigarettes. Lower abuse potential than cigarettes with comparable extent of nicotine delivery.

2.2 Purpose of the Study

The purpose of the study is to evaluate the nicotine pharmacokinetics (PK) profiles of 4 variants of NP 1.0 versus Velo-NP and Zyn-NP following a 30-minute use period. In addition, pharmacodynamic effects (PD), including subjective effects and related behavioral assessments will be evaluated, to provide further insights on NP 1.0 product acceptance and abuse liability. Safety will be assessed throughout the study.

The aim is to evaluate if NP 1.0 can provide an acceptable alternative to smoking cigarettes in terms of both, nicotine delivery and sensorial satisfaction for smokers who would otherwise continue smoking cigarettes.

2.3 Anticipated Benefits and Risks

2.3.1 Anticipated Benefits

Information on health risks associated with smoking and smoking cessation advice will be provided. Subjects who are motivated to quit smoking or using other nicotine/tobacco-containing products during the study will be given the opportunity to continue their smoking cessation attempt and will be referred to appropriate stop smoking services for continuing support and counselling at a higher level. Subjects who participate in this study will also benefit from repeated and detailed health check-ups.

2.3.2 Anticipated Foreseeable Risks due to Study Procedures

The risk of scheduled procedures in the present study (e.g., blood samples) are deemed to be on par with procedures routinely performed during normal or extended health examinations by the subject's healthcare professional. The total volume of blood to be drawn is approximately 340 mL and does not exceed the levels for a standard blood donation. The risks related to blood sampling include for example: excessive bleeding, fainting, hematoma, paresthesia or infection, and those related to the total amount of blood taken over a period of time such as weakness, dizziness or anemia.

2.3.3 Anticipated Foreseeable Risks due to Investigational Product

By product design, NP 1.0 variants are free from the majority of HPHCs associated with heating or burning tobacco, except nicotine.

Due to sensorial and technological differences between NP 1.0 versus cigarettes and the confinement setting, subjects may modify their nicotine uptake.

An adult smoker using NP 1.0 may experience:

- Transient nicotine withdrawal symptoms (e.g., urge to smoke, irritability, anxiety feelings, restlessness, and difficulty to concentrate) similar to cravings observed during smoking cessation
- Transient symptoms suggesting mild nicotine overdose such as stimulatory effects on sympathetic tone (increased blood pressure, increased heart rate), central nervous system (tremor, blunting of emotions, and decreased ability to concentrate), gastric acid secretion, and vomiting.

Support during periods of abstinence from any tobacco and nicotine containing products will be provided.

Further risk mitigation will include:

- Using commonly accepted research and scientific standards (e.g., blood samples not to exceed blood donation standards)
- Medical supervision of all study subjects with follow-up of those who have experienced AEs/serious adverse events (SAEs)

2.3.4 Unforeseeable Risks

The possibility of unforeseeable events/risks will be explained in detail to study subjects. Unexpected product events may lead to unforeseeable risk. Risk mitigation strategies will include close monitoring and medical supervision to detect any unforeseeable risk or safety signals at the earliest time possible.

3 STUDY OBJECTIVES

3.1 Exploratory Objective and Endpoints

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

Endpoints (Day 1 to Day 3)

- 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 (T0), to all subsequent timepoints and extrapolated to infinity [AUC0-5min, AUC0-10min, AUC0-15min, AUC0-20min, AUC0-25min, AUC0-30min, AUC0-35min, AUC0-40min, AUC0-1h, AUC0-3h, AUC0-6h, AUC0-infinity]

2. To describe pharmacodynamic (PD) effects (subjective effects and related behavioral assessments) of 4 variants of Nicotine pouch 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 sale (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}, VAS-S_{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 Product Evaluation Scale and $AUC_{0\text{-infinity}}$ PK endpoint
- Between the item scores of the Sensory questionnaire and AUC0-infinity PK endpoint

5. To describe the extent of nicotine extracted during product use from 4 variants of Nicotine pouch 1, Velo-NP and Zyn-NP. Reporting of this objective will be separate from the main Clinical Study Report.

Endpoint (Day 1 to Day 3)

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

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a single-center, randomized, controlled, open-label, cross-over study in healthy subjects to investigate the nicotine pharmacokinetic profiles of four variants of Nicotine pouch 1.0, compared to Velo-NP and Zyn-NP. In addition, PD effects (subjective effects and related behavioral assessments) will be evaluated to provide further insights on Nicotine pouch 1.0 product acceptance and abuse liability. The study will be conducted with 3 periods and in a 6 sequence-cross-over design.

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

A sufficient number of subjects will be screened to ensure that 24 subjects will be randomized into the study with at least 25% of each sex.

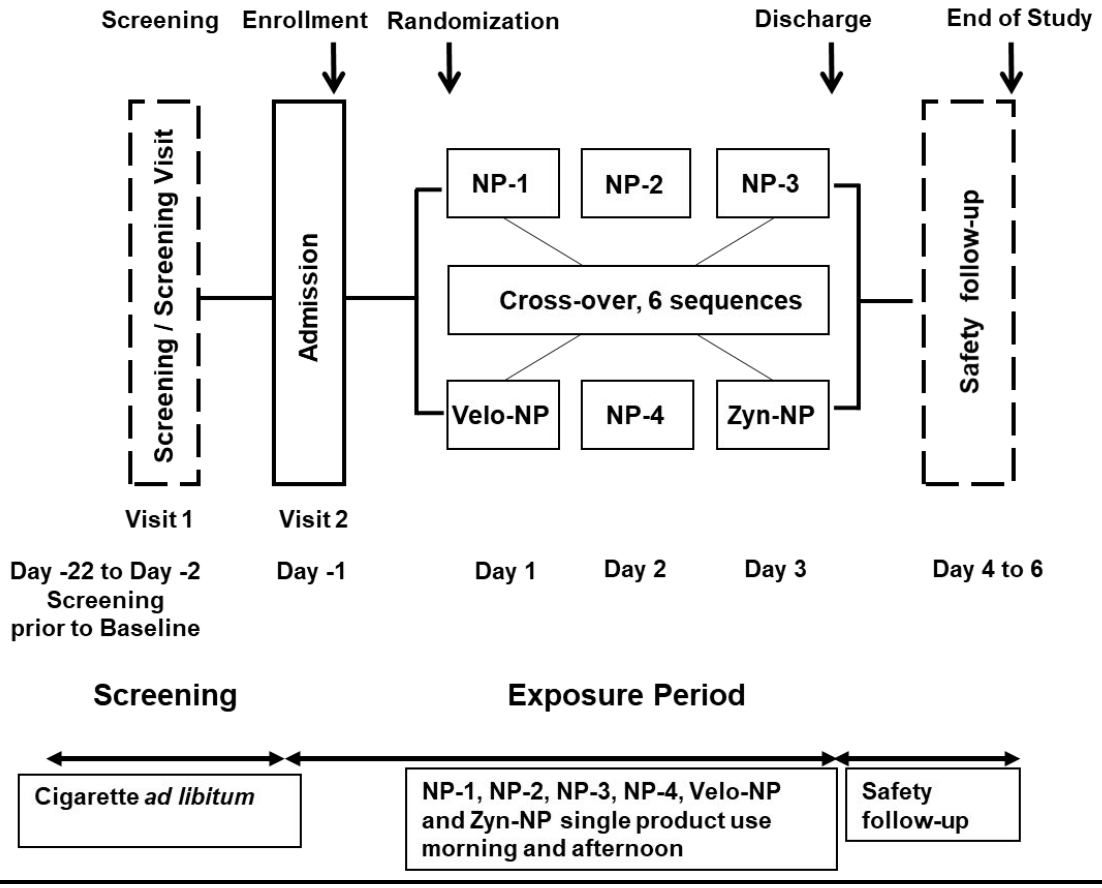

Figure 2 Study Design

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 Nicotine pouch 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 4 variants of Nicotine pouch 1.0, Velo-NP and Zyn-NP during the study after product test will start their confinement period of 3 days.

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.

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 variant of Nicotine pouch 1.0, Velo-NP or Zyn-NP according to randomized product use sequence for 30 minutes (± 1 minute). The used nicotine pouches will be collected for long-term storage to determine the residual nicotine after product use to estimate the amount of nicotine delivered during the 30 minutes use period.

Subjects will complete questionnaires about product evaluation, craving and liking assessments.

The start of product use of the 30-minute 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 at 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.

In the morning on Day 1, 12 blood samples will be collected for determination of nicotine concentration at the following time points in relation to T0 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} or after 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 again will be assessed using a VAS (100 mm going from "strong disliking" to "strong liking" for VAS liking (in the moment), and VAS liking (overall), from "no craving" to "strong craving" for VAS craving, from "not at all" to "extremely" for VAS satisfaction, and from "very unlikely" to "very likely" for VAS intention to use again) 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 Product Evaluation Scale (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 associated with IP use reported by the subjects will be collected and the follow-up of the ongoing AEs/SAEs will be conducted by the study investigational site (section 8.2.6).

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.

4.2 Rationale for Study Design

The minimum age of 21 years old in the inclusion criteria was selected based on the legal age of smoking in the United Kingdom of 18 years; and to account for the 3 years of smoking history.

The goal of this study is to evaluate the nicotine absorption profiles and related PK parameters from four variants of NP 1.0 compared to Velo-NP and Zyn-NP.

The 30 minutes use allow appropriate comparisons between different NP products [14]. The collection of PD data will also allow to explore effects of product liking on PK parameters.

Sampling time points for determination of nicotine concentrations were selected to ensure reliable estimation of PK parameters. In particular, frequent sampling between 20 to 50 minutes after T_0 will be performed in order to reliably assess T_{max}, which is expected to be comparable to what has been described previously e.g., for Zyn NP [14, 18].

The PK of plasma nicotine presents a biphasic profile, with a typical rapid initial disposition half-life ($t_{1/2\alpha}$) of 1.35 hours, followed by a slower terminal elimination half-life ($t_{1/2z}$) of 17 hours [19]. To ensure a complete nicotine washout between each product use, 3 days without product use would have been required (~ 5 x terminal elimination $t_{1/2z}$). Based on

nicotine population PK modeling, it was estimated that nicotine enters in the terminal elimination phase with concentrations decreasing with a terminal elimination rate constant (λ_z) 8 to 10 hours post administration. As a consequence, a minimum of 8 hours of nicotine abstinence has been established in this study prior to T_0 on Day 1 to Day 3. In order to estimate the λ_z three valid data points are needed to fit a regression line including estimation of error. The last data point is potentially not estimable (below LOD). Then four data points are likely required to estimate λ_z. Background-concentration correction will be applied to adjust for carry-over effects with adjustment of baseline values to the estimated $t_{1/2z}$ (or λ_z) which will be derived from additional blood sampling on Day 2 and Day 3 for each subject.

The use of estrogen contraceptive is known to accelerate nicotine clearance by 20% to 30% compared to women who do not take estrogen contraceptive [20]. Therefore, for the purpose of this study, use of hormonal contraception containing estrogens is prohibited. This also applies to hormone replacement therapy.

The activity of CYP2A6 will be measured as this enzyme drives the metabolism of nicotine into cotinine and subsequent metabolites. CYP2A6 activity varies between individuals of the same ethnicity/race and across ethnicity/race due to genetic variations. These genetic differences could be associated with reduced/increased nicotine metabolism [21].

4.3 Appropriateness of Measurements

All laboratory measures utilized for this study are validated and are appropriate for the study assessments. FTND [22, 23] and Product evaluation scale (PES) [24, 25] used in this study are validated and previously published or adapted versions of validated questionnaires.

Cigarette craving will be assessed using a one-item self-reported craving VAS [26], 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). 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 [27]. 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. 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 [28] to meet current regulatory recommendations in human abuse liability of tobacco and nicotine products.

4.4 Study Duration

The entire study per subject will between 8 and 27 days. This will include a screening period of up to 21 days prior to Admission (Day -22 to Day -2), 3 days of confinement after enrollment on Day -1 to discharge on Day 3, (3 overnight stays), and a 3-day Safety follow-up period (from time of Discharge at Day 4 to Day 6). The end of the study (EOS) for a subject is defined as the end of the Safety follow-up period. The end of the whole study corresponds to the individual EOS of the last subject.

5 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.

5.1 Selection of Study Population

5.1.1 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 ICF and is able to understand the information provided in the ICF.	X	
2. Smoking male or female aged between 21 and 65 years inclusive.	X	
3. Subject has smoked continuously for at least the last 3 years prior to the Screening visit.	X	
4. Subject 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
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	

5.1.2 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	
6. 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	

Exclusion Criteria	Screening	Admission (Day -3)
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.

5.2 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 (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 (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 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.
- A sufficient number of subjects are already randomized to the study sequences. In this case, additional subjects (alternates) will be discontinued prior to randomization.

- Violations of eligibility criteria have been determined (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. Should there be the need to discontinue all subjects from one cohort, e.g. all subjects contracted a disease pathogen, subjects for a replacement cohort may be enrolled and randomized.

5.3 Lost to Follow-up

A reasonable attempt will be made to contact all participants needing to complete or resolve post-study activities (e.g., safety laboratory, physical examination, on-going AEs).

Two contacts will be made via contact information provided by the subject (e.g., telephone number, cell phone number, email address), allowing 1 day between attempts for response. The first contact attempt should take place within approximately 1-2 days of the participant's last visit to the investigational site. If contact is not possible, a follow-up letter will be sent to the participant, allowing approximately 5 business days from the time of delivery for a response. A progress note will be added in the data collection system for documentation. After a letter is sent, there should be no additional phone calls unless the participant has attempted to contact the investigational site and a return call attempt is made. If post-study follow-up has not been resolved within approximately 5 business days following delivery confirmation or the letter is not deliverable, the participant is considered lost to follow-up. This is documented in the progress note and outstanding AEs are updated. The date of lost to follow-up corresponds to the date of the end of study of the subject.

The Investigator or designee(s) will declare the subject lost to follow-up if the investigational site lost contact to the subject and the subject has reached the maximum number of study days (27 days).

5.4 Violation of Selection Criteria

Detected violations of eligibility criteria post enrollment may require subjects to be discontinued from the study based on a case-by-case decision of the Investigator.

6 INVESTIGATIONAL PRODUCTS

6.1 Description of Investigational Products

NP 1.0, Velo-NP and Zyn-NP will be provided by the Sponsor.

The distribution and return of investigational products will be controlled by qualified and appropriately trained investigational site staff.

6.1.1 Test Product

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

6.1.2 Comparator Product

Name	Nicotine per pouch	Flavor
Velo-NP	10 mg	Cool mint
Zyn-NP	3 mg	Cool mint

6.1.3 Packaging and Labeling

NP 1.0 will be provided in sealed cans labelled with the required information including, but not limited to, product code and expiry date.

Velo-NP and Zyn-NP are marketed products, packaged and labelled according to manufacturer specifications.

6.2 Use of Investigational Product(s)

Subjects will not be forced to smoke cigarettes or use NP 1.0, Velo-NP and Zyn-NP and will be free to stop NP use at any time of the study.

During the screening period, subjects will be allowed to smoke and use tobacco/nicotine-containing products according to their product use habits except during the procedures of the Screening Visit (section 9.1).

6.2.1 Admission Day (Day -1)

After enrollment, subjects will perform a product test with NP-1 for 30 minutes (± 1 minute). One NP-1 nicotine pouch will be placed between the upper lip and the gum for 30 minutes and subjects will be instructed not to manipulate the pouch with the tongue or lips.

After the product test, subjects will be required to abstain from any nicotine/tobacco containing product use until the first product use on Day 1.

6.2.2 Exposure Period (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 according to randomized product use sequence for 30 minutes (± 1 minute) in the morning and in the afternoon. One nicotine pouch will be placed between the upper lip and the gum for 30 minutes and subjects will be instructed not to manipulate the pouch with the tongue or lips. The same application site should be used for all products.

6.2.3 Day of Discharge (Day 3) and Safety Follow-up Period

Post discharge and during the safety follow-up period, subjects will be free to use any nicotine/tobacco products according to their usual habits.

6.2.4 Stopping Rules for Investigational Product

For safety purposes, using NP 1.0, Velo-NP or Zyn-NP should be temporarily stopped in the event of any signs suggesting nicotine overexposure, *e.g.,* gastrointestinal disturbance (nausea, vomiting, diarrhea, stomach or abdominal pain), cold sweats, headache, dizziness and breathing problems, or any reasons at the discretion of the Investigator.

6.3 Method for Assigning Subjects to Product Sequences

The method for assigning subjects to product sequence is described in section 12.9.1.

6.4 Blinding

The blinding procedure are described in section 12.9.2.

6.5 Investigational Product Accountability and Adherence

6.5.1 Dispensing Investigational Product

From Day -1 until Day 3, one single NP 1.0, Velo-NP or Zyn-NP will be dispensed by the investigational site staff, as per the study design.

Each dispensing of investigational products (IP) to the subject will be recorded in a log.

6.5.2 Storage and Accountability

NP 1.0, Velo-NP and Zyn-NP will be stored in a secured storage place at the investigational site with access limited to the authorized personnel only. The distribution and return of IP will be controlled by qualified and appropriately trained investigational site staff.

6.5.3 Investigational Product Retention

Used NP 1.0, Velo-NP and Zyn-NP will be collected for long-term storage to determine the residual nicotine after product use to estimate the amount of nicotine delivered during the 30 minutes use period.

Unused NP 1.0, Velo-NP and Zyn-NP will be destroyed or returned to the Sponsor upon study completion.

6.5.4 Adherence to Investigational and Comparator Products

Adherence will be ensured by strict distribution and collection of any used and unused NP 1.0, Velo-NP and Zyn-NP by designated investigational site staff.

6.6 Restrictions

6.6.1 Smoking Restrictions

During the Screening period, subjects will be allowed to use any nicotine/tobacco-containing products according to their usual habits except during the procedures of the Screening Visit (section 9.1). Spirometry assessment at Screening will be performed 1 hour after stopping smoking (section 9.1).

From Admission (Day -1) to Discharge (Day 3) or early termination, use of any nicotine/tobacco containing products, except use as per study design of the allocated product will not be permitted.

A nicotine washout period of at least 8 hours should be respected before T_{0M} and T_{0A} of NP use at Day 1 to Day 3.

6.6.2 Dietary Restrictions

A standard diet will be designed for the whole confinement period. For each meal, the caloric and fat content should be controlled to avoid a "high-fat" diet. The FDA guidance on food-effect studies for bioequivalence testing identifies a "high-fat" diet as a diet which contains "approximately 50 percent of total caloric content of the meal [from fat] and is high in calories (approximately 800 to 1000 calories)" [29].

Subjects are not allowed to bring their own food or beverages to the investigational site. Meals will be served as described in section 8.1. Additional light snacks, fruits, and raw vegetables can be distributed to the subjects without restrictions at any time during confinement (except during product use periods) if they comply with the standard diet. Consumption of water is allowed as desired. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed. Subjects should refrain from ingesting foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade from 7 days prior to Day -1 and throughout the study. The same menu and meal schedule will be administered uniformly for all subjects. Subjects should have fasted (black coffee or tea without sugar is possible) for at least 10 hours prior to safety laboratory assessments at Day -1 and on Day 3.

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

6.7 Concomitant Medication

All medication taken within 4 weeks prior to the ICF signature will be considered prior medication. All medication taken from Screening Visit to end of the Safety follow-up period will be considered concomitant medication.

Only progesterone-containing hormonal contraception will be allowed. Hormonal contraception containing estrogens or hormone replacement therapy will be prohibited and subjects will be excluded based on eligibility criteria.

Any medication with an impact on the CYP2A6 metabolism [30] (used as prescription and over-the-counter products), including, but not limited to medications listed in Table 1, must be avoided as CYP2A6 is involved in the nicotine metabolism. To be eligible for the study, any medication with impact on CYP2A6 metabolism must have been discontinued at least 14 days prior to Admission or for at least 5 half-lives (whichever is longer) and should not be used during the entire study until the time of Discharge or early termination. Prior to database lock, concomitant medication will be reviewed for their potential impact on CYP2A6 activity and the study results.

Table 1 Concomitant Medication

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

Use of over-the-counter medication will be restricted from Admission (Day -1) to Discharge or early termination, although exceptions may be made on a case-by-case basis at the discretion of the Investigator.

Use of any other concomitant medication will be evaluated on a case-by-case basis by the Investigator. Any concomitant medication used will be fully documented (section 7.4.2).

7 STUDY PROCEDURES

Investigational site staff performing or recording study assessments must have the appropriate and fully documented training. An overview of study assessments and time points is shown in the schedule of events (Appendix A). Appropriate medical advice will be provided to the subject in case of any medical findings requiring health care. Site personnel will adhere to the site's standard operating procedures (SOPs) for study related procedures. Timing of the different assessments are described in the schedule of events (Appendix A).

7.1 Informed Consent

Subjects will be asked to provide their written consent to participate in the study (section 1.3). Study assessments must only start after the time of ICF signature by the subject.

7.2 Information on the Risk of Smoking and Smoking Cessation Advice and Debriefing on Nicotine pouch 1.0

Subjects will receive 1) information on the risks of smoking, 2) smoking cessation advice, and 3) debriefing on NP 1.0.

The information on the risk of smoking and advice on smoking cessation will take the form of a brief interview according to the WHO recommendations [31]. The goal of the debriefing is to help ensure that subjects have an accurate understanding of NP 1.0 use risks.

Details of the sessions will be recorded in the source document file. This information will be given to the subjects on an individual basis during a face-to-face meeting between the subject and the Investigator or designee or may be given in a group session.

7.3 Support during Abstinence from any Tobacco and Nicotine Containing Products

Subjects will be offered support during periods of abstinence from any nicotine/tobacco containing products during the study by the Investigator and/or investigational site staff. Support resources will include counselling and assistance, entertainment, monitoring of the subject's behavior, AEs.

7.4 Clinical Assessments

7.4.1 Demographic Data

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

7.4.2 Medical History, Concomitant Disease, Prior and Concomitant Medication

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

Prior medication taken within 4 weeks prior to the Screening Visit and any concomitant medication will be documented. Any medication started prior to the Screening Visit and still being taken by the subject will be considered concomitant medication. Medication initiated after the Screening Visit will also be referred to as concomitant medication. The definition of concomitant medication applies to both prescribed and over-the-counter products.

Records of medication taken should include the drug name (preferably both generic and trade name), route of administration (e.g., oral, intravenous), dose and frequency (expressed in metric units, for example, mg, mL, or IU), indication, and the start and, if applicable, the stop date (day, month, and year). Therapy changes (including changes of regimen) during the study have to be documented. If a concomitant medication is still being taken by the subject at the end of the study, this will be recorded in the CRF.

7.4.3 Physical Examination

Physical examinations will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, thyroid gland, chest, lungs, back, abdomen, dentition, gastrointestinal, cardiovascular, musculoskeletal, and neurological systems. The physical examination is to be conducted by the Investigator or designated fully trained representative and assessed as normal, abnormal – not clinically significant or abnormal – clinically significant and recorded into the clinical database.

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

7.4.4 Body Height and Weight and BMI

Body height and weight will be recorded at the Screening Visit and body-mass-index (BMI) will be calculated using the following formula:

$$\text{BMI} = \frac{\text{weight in kilograms}}{\text{height in meters}^2} = \frac{kg}{m^2}$$

The BMI will be used to assess eligibility for enrollment.

7.4.5 Vital Signs

Vital signs (systolic and diastolic blood pressure, respiratory rate and pulse rate) will be measured prior to T_{0M}.

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.

7.4.6 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 [32, 33]. Spirometry predicted values will be standardized to the National Health and Nutrition Examination Survey III predicted set [34].

Assessed parameters will include: FEV_1, FEV_1 % predicted, FVC, FVC % predicted and FEV_1/FVC.

All personnel performing spirometry testing should have the appropriate training and quality control measures should be put into place and be properly documented. The testing will be performed in sitting position after resting for at least 15 minutes and at least 1 hour after smoking cigarettes (Screening Visit).

Any printouts of Spirometry on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents.

7.4.7 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has rested for at least 10 minutes in supine position.

All ECGs will be reviewed on an ongoing basis by the Investigator or designee. The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected according to Fridericia's formula.

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

Any printouts of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents

7.5 Biomarker Assessment

All bioanalytical assays and laboratory assessments will be carried out using validated methods. The bioanalytical methods used will be documented in the respective bioanalytical plans/reports. A list of laboratories is provided in Appendix B.

7.5.1 Biomarkers of Exposure to Nicotine

Venous blood samples will be collected to evaluate plasma nicotine PK profile and determination of terminal elimination half-life.

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

7.5.2 CYP2A6 Activity

CYP2A6 activity drives the metabolism of nicotine to cotinine and subsequent metabolites.

One blood sample will be collected for determination of plasma CYP2A6 activity (cotinine and trans-3'-hydroxy-cotinine) prior to T_0 with NP 1.0. The time of collection of the blood sample must be recorded on the.

7.6 Laboratory Assessments

7.6.1 Clinical Chemistry, Hematology, and Urine Analysis for Safety Panel

Hematology and clinical chemistry analysis will be assessed. Subjects should have fasted for at least 10 hours prior to safety laboratory assessments, except at Screening and early termination where non-fasting samples can be used. Tests will be conducted at a local laboratory (Appendix B). If during the screening period a blood sample is not suitable for analysis (e.g., blood clotting) a re-test should be performed for the specific parameters which are not available. Safety urine analysis will be also assessed.

Parameters to be tested are listed in Table 2.

Table 2 Clinical Laboratory Parameters for Safety Panel

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

7.6.2 Serology

Tests for hepatitis B soluble antigen (HbsAg), hepatitis C virus (HCV antibody) and human immunodeficiency virus (anti-HIV1/2) will be performed at the Screening Visit. In case of positive results, the subject will be referred to appropriate medical care and the results may be reported to heath authorities according to local regulation.

7.6.3 Urine Drug Test

A urine drug screen including testing for alcohol will be performed at the site for screening of:

- amphetamine type substances,
- barbiturates,
- benzodiazepines,
- cannabinoids,
- cocaine,
- opiates, and
- alcohol

In case of a positive urine drug test, a re-test will not be allowed in order to evaluate eligibility. In case of an inconclusive test, a re-test can be performed but this needs to be done immediately after the inconclusive test.

7.6.4 Urine Cotinine Test

A urine cotinine test will be performed to confirm the nicotine/tobacco use status.

The test must detect cotinine with a threshold of ≥ 500 ng/mL. In case of a negative cotinine test, a re-test will not be allowed in order to evaluate eligibility. In case of an inconclusive test, a re-test can be performed but this needs to be done immediately after the inconclusive test.

7.6.5 Urine Pregnancy Test

A urine pregnancy test will be performed for all female subjects. Subjects with a positive urine pregnancy test or unclear results (from two repetitions) before enrollment will be considered as screen failures. In case of any positive pregnancy test, the Investigator or designee will inform the subject about the risks associated with smoking during pregnancy and subjects will be referred to health care facility/health care provider for pregnancy follow-up.

All pregnancies detected during the study must be reported and handled as described in section 8.5. Pregnancies detected after enrollment will lead to discontinuation from the study (section 5.2).

7.7 Sample Handling, Storage, and Shipment

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

Detailed procedures for handling of samples are described in the separate sample handling manual (SHM). Safety laboratory samples will be destroyed as per laboratory local regulations. All other samples will be destroyed post database lock or post finalization of the bioanalytical reports, whichever occurs last. The facility/-ies at which the samples are stored will be informed in writing by the Sponsor when destruction of the samples shall be performed.

7.7.1 Blood Samples

Blood samples will be drawn by qualified and trained site personnel and according to the standard operating procedures (SOPs) at the investigational site.

Since the test for nicotine concentration is highly sensitive, precautions should be taken during blood sampling and processing to prevent the contamination of samples with environmental nicotine.

In total, approximately 340 mL of blood will be collected for this study including samples for determination of plasma nicotine concentrations (approximately 296 mL), CYP2A6 activity (5 mL), and safety laboratory including serology (approximately 37.5 mL). This calculation is based on an individual volume of each sample of 4.0 mL for nicotine PK, 5.0 mL for CYP2A6 analysis, 12.5 mL per safety laboratory assessments, including serology. The total volume of blood drawn will not exceed the levels for a standard blood donation.

Details on the procedures for collection, labeling, handling and shipment of samples are described in the SHM/ laboratory manual.

7.8 Questionnaires

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

7.8.1 Fagerström Test for Nicotine Dependence (FTND, Revised Version)

Level of nicotine dependence will be assessed using the FTND in its revised version [23] as updated in 2012 [35].

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) [35].

7.8.2 Nicotine/Tobacco Product Use History

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. This information will be used as characteristics of the study subjects and to assess their eligibility to participate in the study.

7.8.3 Product Evaluation Scale (PES)

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

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) [24] to conform to rating oral tobacco products [25].

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).
- Psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger).
- Aversion (dizziness, nausea, too much nicotine, bothersome side effects).
- Relief (relief craving, relief withdrawal symptoms, relief urge to smoke, enough nicotine, craving for a cigarette).
- Easy to use (single-item assessment).
- Comfortable using (single-item assessment).
- Concerned about dependence (single-item assessment).

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

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.

7.8.4 VAS Craving Assessment

Cigarette craving will be assessed using a one-item self-reported craving VAS [26], 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).

7.8.5 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 [27].

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.

7.8.6 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 [28] to meet current regulatory recommendations in human abuse liability of tobacco and nicotine products.

7.8.7 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.

7.8.8 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 "not at all" to "extremely".

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.

The main source for AE collection in this study is the face-to-face interview between the subject and study site staff, using open, non-directive questions, as described in section 8.2. It is at the discretion of the Investigator or designee(s) to decide whether needed to document as AEs different symptoms reported in the questionnaires (e.g. Sensory questionnaire or Product Evaluation Scale).

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) is defined as any health-related event which is adverse or unfavorable and which either starts after ICF signature or represents a worsening of a health–related condition that existed at the time of that signature. Careful medical judgment is required to establish whether a clinical finding (including an abnormal laboratory result) is a true AE or just a manifestation of a preexisting health–related condition. An AE may or may not have a causal relationship with the study procedures or with the use of investigational product.

8.1.2 Serious Adverse Events

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

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

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

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

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

Clinical conditions that existed before the start of the period of collection of AEs and are still ongoing at Screening (concomitant disease), and whose severity remained unchanged after that point, should not be considered AEs and should not be captured as such. This includes medical therapies or surgical interventions that had been planned before the start of the period of collection regardless of involving admissions to hospital, if the medical condition to be addressed did not get worse after the start of the collection period.

Otherwise, any medical condition that existed before the start of the period of collection and still ongoing at Screening (concomitant disease) and whose severity increased after that point is to be captured as an AE or SAE, depending on the seriousness criteria met.

8.2 Collection and Reporting of Adverse Events

8.2.1 Collection of Information

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

Any non-serious AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the CRF. SAEs that occur during the study must be documented in the subject's medical record, on the AE CRF, and on the SAE form for recording into the safety database.

Information recorded for AEs/SAEs will include: verbatim description, start and stop dates and times, seriousness, severity (intensity), causal relationship with IP and study procedures, action taken with IP (e.g reduced, not changed), other action taken (e.g., treatment administered, if led to the subject's discontinuation from the study), and outcome (e.g., resolved, stabilized).

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms.

8.2.2 Period of Collection

AEs (including SAEs) will be collected from the time of ICF signature until the individual EOS for each subject.

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

During a 3-day Safety follow-up period new AEs/SAEs associated with IP use will be recorded and ongoing AEs/SAEs will be followed-up by the study site, as described in section 8.2.6.

8.2.3 Intensity of Adverse Event

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

Table 3 Intensity of Adverse Events

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

8.2.4 Relationship to Investigational Product and Relationship to Study Procedures

The Investigator must assess the causal relationship between the exposure to the IP (Nicotine pouch 1.0, Velo-NP and Zyn-NP) and each of the reported AEs, using the classification system and the criteria described below. The same assessment must be made separately to assess the causal relationship between the study procedures and each of the reported AEs:

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

Related: The temporal relationship of the adverse event to IP or study procedure(s) makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.2.5 Expectedness

Any AE assessed as related to the IP (Nicotine pouch 1.0, Velo-NP, Zyn-NP) will be assessed for its expectedness. An AE will be regarded as “unexpected” if its nature or severity is not consistent with information already recorded in section 6.5 of the current Investigator’s Brochure [36].

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

Any non-serious AE that is ongoing at the time of Discharge or early termination will be followed-up by the Investigator during the Safety follow-up period until it has been resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). The follow-up of the ongoing non-serious AEs will be done via a phone call performed at the end of the Safety follow-up period. If the subject is not responding at the first phone call additional two attempts will be made, then subject will be declared lost to follow-up (see section 5.3).

At the end of the 3-day Safety FU Period, all ongoing non-serious AEs will have the outcome documented as "unknown" and will not be followed-up by the Investigator. At the discretion of the Investigator, the subject will be referred to his General Practitioner to have his/her ongoing AEs addressed accordingly.

All SAEs will be followed up by the Investigator or designee after the end of the Safety follow-up period, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition). In case the subject cannot be reached for additional information related to SAE(s), a total 3 attempts should be performed before the subject will be declared as lost to follow-up (see section 5.3).

8.3 Reporting of Serious Adverse Events

Any SAE observed during the period of collection in this study must be reported within 24 hours of first awareness to Sponsor, via email, having the SAE form attached.

As further information regarding an already reported SAE becomes available to any of the parties involved in this study, such follow-up information should be reported on a new SAE report form, marked as a follow-up report and submitted to Sponsor according to the same timelines as described above. The follow-up SAE report form must include the minimum information required for form completion and only changed/new information needs to be specified. Information provided in the follow-up SAE report form supersedes any information that was initially reported.

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

The Investigator or designee is responsible for submitting the relevant reports of SAEs that occur during the study to the IEC, according to local regulations and in accordance with the respective safety management plan (SMP).

8.4 Reporting of Other Events Critical to Safety Evaluations

The other abnormal findings discovered during different clinical assessments (e.g., ECG, physical examination, vital signs, body weight, safety labs results) should be evaluated for clinical significance by the Investigator/designee based on his/her medical judgement. All abnormal clinically significant test results or clinical examination findings should be reported as AEs and handled as described in section 8.2.

8.5 Reporting and Follow–Up of Pregnancies

8.5.1 Period of Collection and Follow-up

Pregnancies detected between the time of signature of the ICF and the time before first exposure to the IP will be considered a reason for screen failure. No pregnancy form will

be filled in that case, however the diagnosed pregnancy must be captured in the screen failure page of the CRF.

Any pregnancy detected after first exposure to the IP must be reported by the Investigator within 24 hours. This also includes pregnancies spontaneously reported to the Investigator after the end of the study for a subject. A dedicated pregnancy form will be used to report reportable cases of pregnancy.

Any pregnancy that was potentially associated with exposure to IP (NP 1.0, Velo-NP, Zyn-NP) will be followed-up until an outcome is reached (e.g., normal delivery, spontaneous abortion, or voluntary termination) and also until 8 weeks after delivery. Any pregnancy complication, adverse pregnancy outcome or maternal complications will be recorded as an AE accordingly.

The procedure outlined in section 8.3 should be followed to collect pregnancy reports and provide any additional/follow-up information to Sponsor.

8.5.2 Reporting of Pregnancies

The Investigator is responsible for informing the responsible IEC of any pregnancy case that was reported during the study, as determined by local regulations.

8.6 Adverse Events Leading to Discontinuation

Subjects who are discontinued from the study because of an AE will undergo the early termination procedures (section 9.7), as soon as practical after discontinuation and will enter the 3-day Safety follow-up period.

Any AEs or SAEs that are ongoing at the end of the Safety follow-up period will be managed as described in section 8.2.6.

8.7 Product Events

Any occurrence of NP 1.0 product events should be actively collected during the study and documented by the study site. Nicotine pouch 1.0 product events will be categorized into:

- Nicotine pouches not extractable from can/sticking together
- Rupture of the nicotine pouch when using
- No release of flavor when using
- No release of nicotine when using, or
- Other

Furthermore, any product event that leads to an AE/SAE will follow the same processes as described in section 8.2.

9 STUDY ACTIVITIES

The schedule of assessment can be found in Appendix A. Measurements not conducted at the exact time point but conducted within the given time window (if applicable) do not constitute a protocol deviation but an accepted variability for the given time point.

In general, if no start time for the procedures is provided, then the procedure can be performed at any time during the day.

The main objective for this study is the evaluation of the plasma concentration-time profile of nicotine and derived PK parameters. Therefore, the collection of blood samples for determination of plasma nicotine concentration should be as close to the schedule time as possible and should take precedence over any other assessments required at the same time.

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

The Screening Visit will be performed within 21 days prior to enrollment at Admission (Day -1). Screening procedures must not be started before study information is given to the subject and the consent form signed by the subjects. Then, screening procedures can be performed in the order deemed most practical. While it is recommended to complete as many screening procedures as possible in one day, it is permissible to complete those over more than one day. Smoking is allowed at the Screening Visit at the discretion of the investigational site.

Screening activities are listed in Table 4.

Table 4 Time Schedule – Screening Visit

Time	Blood Sample	Procedures	Additional Information
Prior to any study procedure		Informed consent process and signature of ICF	
During the visit		Information on the risks of smoking/advice on smoking cessation and debriefing on NP 1.0	Section 7.2
		Nicotine/Tobacco product use history	Section 7.8.2
		FTND questionnaire	Section 7.8.1
		Demographics data	Section 7.4.1
		Medical history/ concomitant diseases	Section 7.4.2
		Prior (within 4 weeks prior to the Screening Visit) and concomitant medication	Section
		Physical examination	Section 7.4.3
		Body height, weight and calculated BMI	Section 7.4.4

Time	Blood Sample	Procedures	Additional Information
		Vital signs	Section 7.4.5.
		ECG	Section 7.4.7
		Spirometry	Section 7.4.6
	X	Clinical laboratory parameters (hematology, clinical chemistry)	Section 7.6.1
		Collection of spot urine for:	
		• Urine analysis safety panel	Section 7.6.1
		• Urine drug test including testing for alcohol	Section 7.6.3
		• Urine cotinine test	Section 7.6.4
		• Urine pregnancy test (all female subjects)	Section 7.6.5
	X	Serology	Section 7.6.2
		Review of inclusion/exclusion criteria based on all relevant assessments	
		AE/SAE recording	

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

If the inclusion and exclusion criteria are met, the investigational site staff will contact the subject to arrange Day -1 visit at site.

9.2 Admission (Day -1)

The assessments performed at Admission are listed in Table 5.

Table 5 Time Schedule – Admission (Day -1)

Time	Blood Sample	Procedures	Additional Information
Before enrollment		Information on the risks of smoking/advice on smoking cessation and debriefing on NP 1.0	Section 7.2
		Nicotine/Tobacco product use history	Section 7.8.2
		Concomitant medication/ concomitant disease status	
		Physical examination	Section 7.4.3
		Vital signs	Section 7.4.5
		ECG	Section 7.4.7
	X	Clinical laboratory parameters (hematology, clinical chemistry)	Section 7.6.1
		Collection of spot urine for:	
		• Urine analysis safety panel	Section 7.6.1
		• Urine drug test including testing for alcohol	Section 7.6.3
		• Urine cotinine test	Section 7.6.4
		• Urine pregnancy test (all female subjects)	Section 7.6.5
After enrollment	X	CYP2A6 activity	Section 7.5.2
After CYP2A6		NP-1 product test	Section 6.2.1
During the visit		AE/SAE recording	Section 8.2
		Product events	Section 8.7

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

9.3 Day 1

The study activities performed on Day 1 are listed in Table 6.

Table 6 Time Schedule – Day 1

Time	Blood Sample	Procedures	Additional Information
Prior to T_{0M}		Randomization	

Time	Blood Sample	Procedures	Additional Information
Prior to T_{0M}		Vital signs	Section 7.4.5
Within 15 minutes prior to T_{0M}		VAS craving	Section 7.8.4
T-1 5 minutes ± 1 minute prior to T_{0M}	X	Blood sampling for baseline nicotine level	Section 7.5.1
Just before T_{0M}		Providing one NP 1.0 or Velo-NP or Zyn-NP	Performed by investigational site staff
Start of product use: T_{0M}		Placing NP 1.0 or Velo-NP or Zyn-NP between the upper lip and gum	Section 6.2.2
T1 after 5 ± 1 minutes	X	Blood sampling for nicotine PK	Section 7.5.1
T2 after 10 ± 1 minutes		VAS craving, VAS liking (in the moment) and VAS satisfaction	Section 7.8.4
T3 after 15 ± 1 minutes			Section 7.8.5
T4 after 20 ± 1 minutes			Section 7.8.6
T5 after 25 ± 1 minutes			
T6 after 30 ± 1 minutes			
T7 after 35 ± 1 minutes			
T8 after 40 ± 1 minutes			
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
T10 after 3 hours ± 5 minutes		VAS liking (overall)	Section 7.8.5
T6 after 30 ± 1 minutes		VAS intention to use again	Section 7.8.7
T10 after 3 hours ± 5 minutes			
After 30 minutes of product use		Collection of used NP 1.0, Velo-NP or Zyn-NP	
T9 after 1 hour ± 5 minutes		Product evaluation scale	Section 7.8.3
		Sensory questionnaire	Section 7.8.8
Within 15 minutes prior to T_{0A}		VAS craving	Section 7.8.4
T-1 5 minutes ± 1 minute prior to T_{0A}	X	Blood sampling for baseline nicotine level	Section 7.5.1

Time	Blood Sample	Procedures	Additional Information
Just before T_{0A}		Providing 1 NP 1.0 or Velo-NP or Zyn-NP	Performed by investigational site staff
Start of product use: T_{0A}		Placing NP 1.0 or Velo-NP or Zyn-NP between the upper lip and gum	
T1 after 5 ± 1 minutes	X	Blood sampling for nicotine PK	Section 7.5.1
T2 after 10 ± 1 minutes		VAS craving, VAS liking (in the moment) and VAS satisfaction	Section 7.8.4
T3 after 15 ± 1 minutes			Section 7.8.5
T4 after 20 ± 1 minutes			Section 7.8.6
T5 after 25 ± 1 minutes			
T6 after 30 ± 1 minutes			
T7 after 35 ± 1 minutes			
T8 after 40 ± 1 minutes			
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
T10 after 3 hours ± 5 minutes		VAS liking (overall)	Section 7.8.5
T6 after 30 ± 1 minutes		VAS intention to use again	Section 7.8.7
T10 after 3 hours ± 5 minutes			
After 30 minutes of product use		Collection of used NP 1.0, Velo-NP or Zyn-NP	
T9 after 1 hour ± 5 minutes		Product evaluation scale	Section 7.8.3
		Sensory questionnaire	Section 7.8.8
During the visit		AE/SAE recording	Section 8.2
		Product events	Section 8.7

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

9.4 Day 2

The study activities performed on Day 2 are listed in Table 7.

Table 7 Time Schedule – Day 2

Time	Blood Sample	Procedures	Additional Information
Prior to T_{0M}		Randomization	
Prior to T_{0M}		Vital signs	Section 7.4.5
Within 15 minutes prior to T_{0M}		VAS craving	Section 7.8.4
T-1 5 minutes ± 1 minute prior to T_{0M}	X	Blood sampling for baseline nicotine level	Section 7.5.1
Just before T_{0M}		Providing one NP 1.0 or Velo-NP or Zyn-NP	Performed by investigational site staff
Start of product use: T_{0M}		Placing NP 1.0 or Velo-NP or Zyn-NP between the upper lip and gum	Section 6.2.2
T1 after 5 ± 1 minutes	X	Blood sampling for nicotine PK	Section 7.5.1
T2 after 10 ± 1 minutes		VAS craving, VAS liking (in the moment) and VAS satisfaction	Section 7.8.4
T3 after 15 ± 1 minutes			Section 7.8.5
T4 after 20 ± 1 minutes			Section 7.8.6
T5 after 25 ± 1 minutes			
T6 after 30 ± 1 minutes			
T7 after 35 ± 1 minutes			
T8 after 40 ± 1 minutes			
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
T10 after 3 hours ± 5 minutes		VAS liking (overall)	Section 7.8.5
T6 after 30 ± 1 minutes		VAS intention to use again	Section 7.8.7
T10 after 3 hours ± 5 minutes			
After 30 minutes of product use		Collection of used NP 1.0, Velo-NP or Zyn-NP	
T9 after 1 hour ± 5 minutes		Product evaluation scale Sensory questionnaire	Section 7.8.3 Section 7.8.8
Within 15 minutes prior to T_{0A}		VAS craving	Section 7.8.4

Time	Blood Sample	Procedures	Additional Information
T-1 5 minutes ± 1 minute prior to T_{0A}	X	Blood sampling for baseline nicotine level	Section 7.5.1
Just before T_{0A}		Providing 1 NP 1.0 or Velo-NP or Zyn-NP	Performed by investigational site staff
Start of product use: T_{0A}		Placing NP 1.0 or Velo-NP or Zyn-NP between the upper lip and gum	
T1 after 5 ± 1 minutes	X	Blood sampling for nicotine PK	Section 7.5.1
T2 after 10 ± 1 minutes	X	VAS craving, VAS liking (in the moment) and VAS satisfaction	Section 7.8.4
T3 after 15 ± 1 minutes	X		Section 7.8.5
T4 after 20 ± 1 minutes	X		Section 7.8.6
T5 after 25 ± 1 minutes	X		
T6 after 30 ± 1 minutes	X		
T7 after 35 ± 1 minutes	X		
T8 after 40 ± 1 minutes	X		
T9 after 1 hour ± 5 minutes	X		
T10 after 3 hours ± 5 minutes	X		VAS craving and VAS satisfaction only
T11 after 6 hours ± 5minutes	X		VAS craving and VAS satisfaction only
T10 after 3 hours ± 5 minutes	X	VAS liking (overall)	Section
T6 after 30 ± 1 minutes	X	VAS intention to use again	Section 7.8.7
T10 after 3 hours ± 5 minutes			
After 30 minutes of product use		Collection of used NP 1.0, Velo-NP or Zyn-NP	
T9 after 1 hour ± 5 minutes		Product evaluation scale	Section 7.8.3
		Sensory questionnaire	Section 7.8.8
T1z after 8 hours ± 5 minutes	X	Blood sampling for nicotine terminal elimination	
T2z after 12 hours ± 5 minutes	X	Blood sampling for nicotine terminal elimination	
During the visit		AE/SAE recording	Section 8.2
		Product events	Section 8.7

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

9.5 Day 3

The study activities performed on Day 3 prior to the time of discharge are listed in Table 8.

Table 8 Time Schedule – Day 3 (Discharge)

Time	Blood Sample	Procedures	Additional Information
	X	Clinical laboratory parameters (hematology, clinical chemistry)	Section 7.6.1
		Vital signs	Section 7.4.5
Within 15 minutes prior to T_{0M}		VAS craving	Section 7.8.4
T-1 5 minutes ± 1 minute prior to T_{0M}	X	Blood sampling for baseline nicotine level	Section 7.5.1
Just before T_{0M}		Providing one NP 1.0 or Velo-NP or Zyn-NP	Performed by investigational site staff
Start of product use: T_{0M}		Placing NP 1.0 or Velo-NP or Zyn-NP between the upper lip and gum	Section 6.2.2
T1 after 5 ± 1 minutes	X	Blood sampling for nicotine PK	Section 7.5.1
T2 after 10 ± 1 minutes		VAS craving, VAS liking (in the moment) and VAS satisfaction	Section 7.8.4
T3 after 15 ± 1 minutes			Section 7.8.5
T4 after 20 ± 1 minutes			Section 7.8.6
T5 after 25 ± 1 minutes			
T6 after 30 ± 1 minutes			
T7 after 35 ± 1 minutes			
T8 after 40 ± 1 minutes			
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
T10 after 3 hours ± 5 minutes		VAS liking (overall)	Section 7.8.5
T6 after 30 ± 1 minutes		VAS intention to use again	Section 7.8.7

Time	Blood Sample	Procedures	Additional Information
T10 after 3 hours ± 5 minutes			
After 30 minutes of product use		Collection of used NP 1.0, Velo-NP or Zyn-NP	
T9 after 1 hour ± 5 minutes		Product evaluation scale	Section 7.8.3
		Sensory questionnaire	Section 7.8.8
Within 15 minutes prior to T_{0A}		VAS craving	Section 7.8.4
T-1 5 minutes ± 1 minute prior to T_{0A}	X	Blood sampling for baseline nicotine level	Section 7.5.1
Just before T_{0A}		Providing 1 NP 1.0 or Velo-NP or Zyn-NP	Performed by investigational site staff
Start of product use: T_{0A}		Placing NP 1.0 or Velo-NP or Zyn-NP between the upper lip and gum	Section 6.2.2
T1 after 5 ± 1 minutes	X	Blood sampling for nicotine PK	Section 7.5.1
T2 after 10 ± 1 minutes		VAS craving, VAS liking (in the moment) and VAS satisfaction	Section 7.8.4
T3 after 15 ± 1 minutes			Section 7.8.5
T4 after 20 ± 1 minutes			Section 7.8.6
T5 after 25 ± 1 minutes			
T6 after 30 ± 1 minutes			
T7 after 35 ± 1 minutes			
T8 after 40 ± 1 minutes			
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 30 minutes of product use		Collection of used NP 1.0, Velo-NP or Zyn-NP	
T9 after 1 hour ± 5 minutes		Product evaluation scale	Section 7.8.3
		Sensory questionnaire	Section 7.8.8
Between 2 hours after T_{0A} and Discharge		Collection of spot urine for: • Urine analysis safety panel • Urine pregnancy test (all female subjects)	 Section 7.6.1 Section 7.6.5

Time	Blood Sample	Procedures	Additional Information
		Concomitant medication/concomitant disease status	
		Physical examination	Section 7.4.3
		ECG	Section 7.4.7
During the visit		Information on the risk of smoking/advice on smoking cessation and debriefing on Nicotine pouch 1.0	Section 7.2
During the visit		AE/SAE recording	Section 8.2
		Product events	Section 8.7
		Discharge	

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

9.6 Safety Follow-Up Period

After discharge at Day 3, the subjects will enter a 3-day Safety follow-up period during which AE/SAEs associated with IP use reported by the subjects will be collected and the follow-up of AEs/SAEs will be conducted by the study investigational site as described in section 8.2.6.

9.7 Early Termination Procedures

When a subject is discontinued from the study, all early termination procedures listed in Table 9 are performed unless the subject refuses to perform the assessments or the procedures have already been performed during that study day. Early termination procedures are to be performed only for subjects who have been exposed to investigational products. After the date of termination, the subject will enter into the 3-day Safety follow-up period.

Table 9 Early Termination

Blood Sample	Procedures	Additional Information
X	Clinical laboratory parameters (hematology, clinical chemistry)	Section 7.6.1
	Urine analysis safety panel	Section 7.6.1
	Urine pregnancy test (all female subjects)	Section 7.6.5
	Vital signs	Section 7.4.5
	ECG	Section 7.4.7
	Physical examination	Section 7.4.3
	Information on the risks of smoking/advice on smoking cessation and debriefing on NP 1.0	Section 7.2
	AE/SAE, concomitant medication recording	Section 8.2
	Product events	Section 8.7

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

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

A Clinical Research Associate ("Monitor") from an independent contract research organization (CRO) not involved with the study site will be responsible for the monitoring of the study. Monitoring will be performed according to the CRO's SOPs and as per the agreed monitoring plan with the Sponsor.

Before the first subject is screened and included in the study, an Investigator meeting/site initiation visit will be conducted. During this meeting/visit, the general training of the study procedures and specific training on selected procedures will be performed and documented. All activities to be conducted will be described in the monitoring plan.

During the study, the Monitor will have regular contact with the investigational site, including routine monitoring visits. The frequency and purpose of the monitoring visits will be defined in the monitoring plan agreed with the Sponsor.

The Investigator or designee shall permit the Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator or designee shall access medical records for the Monitor so that entries in the CRFs may be verified. The Investigator or designee, as part of their responsibilities, is expected to ensure that the study adheres to GCP requirements.

The Investigator, or a designated member of the Investigator's staff, must be available during the monitoring visit to review the data and resolve any queries and to allow direct access to the subject's records for source data verification.

The Monitor and the Sponsor's personnel will be available between visits, should the Investigator or other staff at the investigational site need information and/or advice.

Communication by telephone, mail and e-mail may be used as needed to supplement investigational site visits. The Investigator and study personnel will cooperate with the Monitor, provide all appropriate documentation and will be available to discuss the study.

10.2 Training of Staff

Prior to the screening of the first subject, an Investigator Meeting/Study Initiation Visit will be held. During this meeting/visit, the Sponsor or its authorized representative will discuss the requirements of the clinical study protocol and related documents and will also provide training to the relevant systems and other study-specific procedures. The activities of this meeting/visit will be described in the monitoring plan.

Further to the Site Initiation Visit, the Investigator or designee will ensure that appropriate training relevant to the study is regularly provided to all staff involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely

manner to the staff. The Investigator or designee will maintain a record of all individuals involved in the study.

10.3 Audits and Inspections

Good Clinical Practice regulations require independent inspections of clinical program activities. Such inspections may be performed at any time before, during and/or after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or IEC/IRB may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data was recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines and any applicable regulatory requirements. The Investigator or designee will contact the Sponsor or the authorized representative immediately if contacted by a regulatory agency about an inspection at their investigational site.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative and/or regulatory agencies. By signing this protocol, the Investigator or designee understands and agrees to provide access to the necessary documentation and files.

11 DATA MANAGEMENT ACTIVITIES

All data management activities will be described in detail in the data management plan (DMP) and documents specified therein.

11.1 Data Capture

11.1.1 Case Report Forms and Study Records

CRFs are produced by the CRO responsible for Data Management activities (DM-CRO), stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between DM-CRO and the Sponsor (e.g., CD, flash drive, SFTP). This will be documented in the DMP). The subject questionnaires will be completed directly by the subject. Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol in the source documents and DM-CRO will enter the data into the CRF, in accordance with the CRF Completion Guidelines.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. The CRF must be signed by the Investigator to attest that the data contained in the CRF are true and accurate. Any correction made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. The CRF for each subject will be checked against the source documents at the investigational site by the Monitor. Instances of missing or unclear data will be discussed with the Investigator for resolution. A CRF will be generated for all subjects that sign the ICF.

11.1.2 Protocol Deviations

Protocol deviations are defined as any departure from the procedures defined in this document, 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.

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 DMP.

Information from the source documents will represent the primary source of protocol deviations. Information following investigational site monitoring and other manual reviews will be documented in the investigational site visit reports, follow-up letters, audit documentation, or other manual review and will be recorded and tracked in the CTMS or other approved format. Telecommunications and other verbal communications regarding deviations will be considered and handled as important communication, documented and tracked as protocol deviations, as necessary.

Individual entries for protocol deviations that are recorded in the CTMS, or other approved format, following investigational site monitoring and other manual reviews, will be reviewed against the individual data points in the database. The overall procedure for managing protocol deviations are defined in the SOPs and study specific procedures of the DM-CRO. All deviations will be reviewed, as defined at study start, to identify trends to improve monitoring and/or potential impact on the statistical analysis.

11.2 Data Handling

All study data will be managed by the DM-CRO. The overall procedures for quality assurance of clinical study data are described in the SOPs of the DM-CRO. The DM-CRO will prepare the DMP that will be approved by the Sponsor, prior to the start of the study, i.e., First Subject Screened. This document will describe, in detail, the procedures and processes related to data management.

All data of all subjects that are enrolled will be captured and stored in the study database. For screen failures, only the following information should be captured: date/time of ICF signature, date of birth, sex, race, AEs, date and reason for screen failure.

All data collected during the study is property of the Sponsor, irrespective of the location of the database and the DM-CRO.

The sponsor should ensure that the Investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

The Investigator should have control of all essential documents and records generated by the Investigator/investigational site before, during and after the study.

Additional details are covered in the DMP.

11.2.1 Data Verification

The data will be verified as defined in the DMP and data validation plan (DVP). Data clarification forms (DCFs) will be issued to the investigational site for discrepant or missing data.

All changes to data will be captured in the database with a comprehensive audit trail.

11.2.2 Coding

Adverse events, concomitant diseases, medical/surgical history, prior/concomitant medication will be classified according to the terminology of the latest version of the following dictionaries, at time of coding the first entry:

Adverse events, concomitant disease, medical/surgical history:	Medical Dictionary for Regulatory Activities (MedDRA®)
Prior/concomitant medication:	WHO Drug Dictionary Enhanced and Anatomical Therapeutic and Chemical classification system

11.2.3 Database Lock

When all outstanding data management issues have been resolved and all validation, quality review and cleaning activities are complete as defined in the DMP, the Sponsor organizes a data review and ensures that the resolution of all raised queries and quality control of the changed data are performed by the CRO before approving the database locked.

Any changes to the database after that time can only be made by written agreement between the Sponsor and the data management and statistical teams at the CRO. Any changes must be documented in the database log file and if these impact the study analysis the PMP S.A. process for a database unlock may be requested.

The study database will be transformed into a Clinical Data Interchange Standards Consortium (CDISC) compliant format and transferred to the Sponsor as specified in the DMP and defined in the data transfer agreement. The clinical data will adhere to the CDISC Study Data Tabulation Model (SDTM) Data Structure Specifications.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Full details of the statistical analysis will be described in the Statistical Analysis Plan (SAP). The following statistical analyses will not be performed prior to the finalization of the SAP. Any changes to the planned statistical methods will be documented in the SAP and CSR. The statistical evaluation will be performed using SAS®, version 9.2 or higher.

12.1.1 Stratification Criteria

The sample enrollment will enforce at least 25% of each sex, therefore demographics, baseline characteristics, PK and PD parameters analyses will be stratified by sex, as well as unstratified, as detailed in the SAP.

12.1.2 Definitions for Statistical Data Analysis

For PK and PD analyses, baseline will be defined as the last assessment prior to T_0 (5 minutes prior to T_0) for each study day of exposure.

Nicotine PK parameters (e.g., T_{max}, $C_{max, ...}$will be derived from background-corrected nicotine concentrations.

12.1.3 Descriptive Statistics

All data will be presented in listings, ordered by randomized sequence, subject, and time point unless otherwise specified.

Continuous endpoints will be summarized with descriptive statistics including number of subjects (n), number and percent of subjects with missing data, arithmetic means and standard deviations (mean and SD), median, first and third quartiles, minimum and maximum, and change from baseline.

For log normally distributed endpoints, geometric mean, geometric CV, confidence interval of the geometric mean, and percent change from baseline will be presented additionally.

Nominal categorical variables will be summarized by frequency statistics (number and percentage), including the number of missing data as a category.

Ordinal categorical data (e.g., T_{max}) will be summarized by number of subjects (n), number and percent of subjects with missing data, median, first and third quartiles, and minimum and maximum.

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

In general, missing data will not be imputed in this study, due to the nature of the measurements and the short periods of exposure and use. However, for questionnaire data, total scores and domain or subscale scores may use a certain degree of imputation by averaging across individual item scores. Further details will be provided in the SAP.

Nicotine concentrations outside detection limits will be substituted using the following rules:

- 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.

Handling of missing answers to questionnaires will be described in the SAP.

12.2 Analysis Sets

The following analysis sets will be used for the data analyses.

12.2.1 Screened Population

The screened population consists of all subjects who underwent screening.

12.2.2 Safety population (SAF)

The safety population (SAF) will consist 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 regardless of whether or not they are enrolled in the study).

12.2.3 PK Population

The PK Population is a subset of the Safety population 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 the SAP, which have an impact on evaluability of the main objective will be included in the PK population.

12.3 Disposition of Subjects

Disposition of subjects will be summarized in the SAF population by reporting the number of subjects screened, enrolled, enrolled, and exposed to NP, randomized, completed, and discontinued the study with discontinuation reasons.

12.4 Protocol Deviations

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.

12.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the SAF and PK populations using the appropriate summary statistics as described in section 12.1.3.

Summaries will include sex, age, height, weight, BMI, nicotine/tobacco product use history, FTND, CYP2A6 activity and other endpoints that are only captured prior to product use.

12.6 Exploratory Analysis

12.6.1 Descriptive Statistics

Descriptive statistics will be performed on Background-Corrected Plasma Nicotine Concentrations, Observed Plasma Nicotine Concentrations, and PK, PD parameters in the PK population, by NP product and for all the planned timepoints, as described in section 12.1.3.

Summaries will be produced overall and stratified as described in section 12.1.1.

12.6.2 Primary Estimand Analysis

The primary estimand is defined as following:

Product Use Under Evaluation: 30 minutes product use period.

Target Population: Healthy adult smokers, who:

- Satisfy all inclusion/exclusion criteria (see section 5.1)
- Tolerate NP, based on a 30-minute product test at Admission (Day -1) after which subject have not, or have not been, discontinued.

Variables of Interest: C_{max}, T_{max}, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}10min}$, $AUC_{0\text{-}15min}$, $AUC_{0\text{-}20min}$, $AUC_{0\text{-}25min}$, $AUC_{0\text{-}30min}$, $AUC_{0\text{-}35min}$, $AUC_{0\text{-}40min}$, $AUC_{0\text{-}1h}$, $AUC_{0\text{-}3h}$, $AUC_{0\text{-}6h}$, $AUC_{0\text{-}infinity}$.

Intercurrent Events:

- Subject's non-adherence with 30 minutes (± 1 minute) IP use: If the subject uses other tobacco or nicotine product than the planned IP, or if the subject does not adhere with the planned IP use of 30 minutes (± 1 minute), the variables of interest from the related sequence's period will be set to missing and handled as MAR.
- Subject's non-adherence with abstinence periods: If the subject has used any nicotine or tobacco product during an abstinence period, the subject's variable of interest data from the related sequence's period will be set to missing and handled as MAR.
- Subject's discontinuation. The corresponding subject's variable of interest missing data will be handled as MAR.

Population-Level Summary Statistic:

- Geometric means ratios for C_{max}, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}10min}$, $AUC_{0\text{-}15min}$, $AUC_{0\text{-}20min}$, $AUC_{0\text{-}25min}$, $AUC_{0\text{-}30min}$, $AUC_{0\text{-}35min}$, $AUC_{0\text{-}40min}$, $AUC_{0\text{-}1h}$, $AUC_{0\text{-}3h}$, $AUC_{0\text{-}6h}$, $AUC_{0\text{-}infinity}$.
- Median differences for T_{max}.

12.6.2.1 Main Analysis

Missing Data Strategy

The outcome data that will be missing or set to missing following an intercurrent event, will be assumed to be missing at random (MAR) and will be handled through model-based restricted maximum likelihood (REML) estimates.

Statistical Model

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

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

An 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 matrix will be used (in this order) until one converges. Variance Components, Compound Symmetry, and finally no repeated statement.

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% confidence intervals (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 10.

Table 10 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.

12.6.2.2 Sensitivity Analysis

In case the plasma concentrations cannot be background-corrected in 2 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.

12.6.2.3 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 study day will be excluded from the analysis.

An analysis of covariance (ANCOVA) will be conducted by product use. The PK parameters will be transformed in the natural logarithmic scale. The model will include terms for sequence, period and a PD parameters mentioned in the objective 4. 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.

Another analysis of covariance (ANCOVA) will be conducted similarly at the exception that it will be performed overall using mixed effects ANCOVA where the model will include additionally the subject as a categorical random effect to model the within subject correlations.

A multivariate analysis will be performed to analyze the joint effect of nicotine concentration, PH and moisture. The PK parameters will be transformed in the natural logarithmic scale. The model will include be adjusted for product use, sequence, period, and covariates encoded as low and high for nicotine concentration, PH level and moisture percentage. The results of this analysis will be presented for all products. The output will contain regression coefficients and their confidence intervals for factors of interests. Further details will be provided in the SAP.

12.7 Safety Analysis

In general, all safety data will be listed and tabulated in the Safety population using the approach described in section 12.1.3. Safety variables collected during exposure period will also be reported by sequence.

AE data will serve for the assessment of safety. Other safety variables monitored in this study include: incidence of NP 1.0 product events including malfunction/misuse; vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); ECG data; clinical chemistry, hematology, and urine analysis safety panel; concomitant medication.

The number and percentage of subjects with AEs, SAEs, and product events will be tabulated by system organ class and preferred term. Summaries will also be presented for AEs leading to 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 include the number of subjects experiencing an event and the number of events.

Safety laboratory assessments are performed on Day -1 and Day 3 in the morning prior to product use (). Any lab related AEs on Day 3 will be assigned to the product used on the previous day.

Summary tables showing actual values and change from baseline of clinical findings will be provided for ECGs, vital signs, and laboratory parameter. Descriptive statistics will be summarized by period for ECG and vital signs and by Day for laboratory parameters, ECG and vital signs.

12.8 Interim Analysis

No interim analysis will be done.

12.9 Measures to Control Bias

12.9.1 Method for Assigning Subjects to Study sequences

The study will be conducted with 6-period and 6 sequences in a cross-over Williams design [37]. A Williams design is an orthogonal Latin squares design with balanced property [38]. On day -1, subjects will be randomized to one of the six study sequences. Details about the randomization process will be included in the Data Management Plan (DMP).

A minimum quota of each sex will be applied to ensure they represent at least 25% of the total study randomized population.

12.9.2 Blinding

This is an open-label study. However, the subjects will be blinded to the randomized sequence. Subjects will be blinded to the products they will receive.

The PMP study statistician and the PMP clinical scientist will be blinded up to the end of the data review process as summarized in Table 11.

Table 11 Description of Blinded Study Personnel

Blinded Study Personnel	End of Blinding Period
PMP and CRO Study Statisticians	After the SAP finalization[a].
PMP Clinical Scientist	After the SAP finalization[a]. Can be actively un-blinded when appropriate.

a. As part of the PMP S.A. quality control (QC) activity, a data review will be performed before database lock. Data listings will be reviewed by the CRO and PMP S.A., with no access to the product information for blinded data review team members. Full details will be available in the data review plan.

12.9.3 Study Significance Level

Not applicable

12.9.4 Multiple Testing Procedures

It is an exploratory study thus no adjustment for multiplicity will be done. When inference will be performed, point estimate and 95% confidence interval (95% CI) will be computed.

12.9.5 Determination of Sample Size and Power Consideration

The sample size is empirically based as there are no considerations for statistical hypothesis.

A total of 24 subjects is expected to be sufficient to obtain a precision of 15% or less on the NP-1: Velo-NP C_{max} ratio.

The precision has been determined using the following geometric coefficient of variation (GCV) and within subjects correlation assumptions for C_{max}:

- For all products the GCV of C_{max} is assumed to be 40%. [1]
- The correlation within subjects on log-transformed data is assumed to be 0.7. It has been derived as the correlation that would explain the width of the confidence interval of the C_{max} difference between the Zyn and Velo-NP product, as compared to the confidence interval of the C_{max} of Zyn-NP and Velo-NP product as described in [16].

The precision has been determined using 10,000 simulations performed with SAS®.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

13.1.1 Investigator

Investigator:	[redacted], MD [redacted]

13.1.2 Sponsor

The list of sponsor personnel will be provided as a separate document.

13.1.3 Other Responsibilities

Project Management:	[redacted]
Monitoring:	[redacted]
Data Management:	[redacted]
Pharmacokinetic Analyses:	[redacted]
Statistical Analyses:	[redacted]

All duties and responsibilities transferred by the Sponsor to the above listed CROs will be defined in an agreement signed between the relevant two parties.

Any SAEs or pregnancies will be handled as described in section 8.3.

Details of the laboratories conducting the clinical safety laboratory services and bioanalyses are shown in Appendix B.

13.2 Subject Recruitment

Subjects will be recruited from the volunteers' database maintained by the CRO. This database contains a pool of volunteers that are contacted whenever necessary to enroll subjects in a new study. Before the start of the new study, the Investigator and other relevant staff discuss with the volunteers' recruiter the study recruitment needs and specific requirements. On the basis of this information, the volunteers' recruiter queries the database, contacts potential volunteers to propose the study and evaluate their interest and availability. In addition to the volunteer's database, IEC-approved advertisement will be used. New subjects often call or email the CRO asking to become a research volunteer, after hearing of the clinical site activities from other volunteers or friends or after checking the company web site. The CRO and its clinical site have detailed SOPs on the recruitment process.

13.3 Subject Confidentiality

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

The name of the subjects participating in this study will be kept confidential. Subjects will be identifiable by the Sponsor (or Sponsor's authorized representative) on CRFs and other documents by their subject (or randomization) number/code, sex, and age, but not by name, initial, or any other details relating to identifiable person (e.g., address, social security number, medical chart number, etc.). The assignment of a subject number/code for subject identification will be based on the appropriate data protection rules.

Any documents that allow full identification of the subject (e.g., the subject's signed ICF) must be maintained in confidence by the Investigator. If any document relating to this study shows a subject's name or any other details relating to an identifiable person (e.g., address, social security number, medical chart number, etc.), the name or other identifiable details must be obscured before a copy of that document is supplied to the Sponsor or the Sponsor's authorized representative.

13.4 Access to Source Documentation

Subjects will be informed that, during the study, the Sponsor, any authorized representatives of the Sponsor, IEC/IRB or regulatory authorities may inspect their medical records and source documentation to verify the information collected and ensure that all personal information made available for inspection is handled in the strictest confidence and in accordance with national and local data protection and privacy legislation.

The Investigator and all investigational site staff involved with the study must permit direct access to source data/documents for study related monitoring, audits, IEC/IRB review and regulatory inspection(s).

13.5 Record Retention

All records of data, source data and source documents (original records or certified copies), in any form (including, but not limited to, written, electronic, magnetic, optical records and scans and ECGs) that describe or record the methods, conduct, and/or results of the study, the factors affecting the study and the actions taken will be maintained by the investigational site for the study, as required by ICH GCP [1] and any other applicable local or national regulations.

Essential study documents/records, which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, are described in section 8 of the ICH GCP Guideline [1].

Essential documents must be retained by the Investigator for a minimum of:

- At least 15 years after completion or discontinuation of the study.

However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor.

Examples of essential records/documents include, but are not limited to:

- Signed informed consent documents for all subjects and master ICF.
- Subject identification code list, Screening log and Enrollment log (if applicable).
- Record of all communications between the Investigator and the IEC/IRB, composition of the IEC/IRB.
- Record of all communications/contact between the Investigator, the Sponsor, and its authorized representatives.
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, CVs, and their signatures.
- CRFs, study specific questionnaires (and associated data/scoring).

- AE reports and details of follow-up investigations, details of concomitant medication.
- All other source documents (e.g., ECGs, consultation reports, physical examination and laboratory records) or any electronically captured study source data.
- Clinical laboratory reports, laboratory normal ranges.
- Original medical/hospital records, if applicable (the medical files of study subjects must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital or study site).
- Record of any body fluids or tissue samples collected and retained.
- IP Accountability Logs, dispensing records.
- Information regarding subjects' discontinuation and any follow-up.

It is the responsibility of the Sponsor to inform the Investigator/study site as to when these documents no longer need to be retained.

The Investigator/study site must take measures to prevent accidental or premature destruction of these documents.

If an Investigator wishes to assign the study records to another party or move them to another location, the Sponsor must be notified in advance. The Investigator must obtain written approval from the Sponsor before destruction of any records. Normally, these records will be held in the Investigator's archives. If an Investigator is unable to meet this obligation, they must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

The Sponsor or Sponsor's authorized representative will maintain documentation relating to the study as long as the IP is on the market, and/or for 15 years after the CSR has been finalized.

13.6 Clinical Study Report

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

The CSR will be written based on standards of the ICH Guideline for the "Structure and Content of Clinical Study Reports" [39]. In certain circumstances, an abbreviated CSR may be acceptable. Submission of the CSR to the IEC/IRB will be complied with as requested by local requirements.

13.7 Financial Disclosure

Investigators and any designees are required to provide financial disclosure information to the Sponsor. In addition, the Investigators and designees must provide the Sponsor with a

commitment to promptly update this information if any relevant changes occur during the study and for one year following the completion of the study.

13.8 Publication and Disclosure Policy

This document contains information that is confidential and proprietary to the Sponsor. This information is being provided solely for the purpose of evaluation and/or conducting this study for the Sponsor. Disclosure of the content of this document is allowed only to study personnel, IEC/IRB, or duly authorized representatives of regulatory agencies for this purpose under the condition that confidentiality is maintained. The contents of this document may not be used in any other study, disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, prompt notice must be given to the Sponsor prior to any such disclosure.

The study will be registered and published in a WHO primary register or at www.clinicaltrials.gov.

13.9 Insurance

The Sponsor is responsible for AEs and health damage of the subjects that are associated with the investigational products which are used during the study, except for AEs and health damage of the subjects caused by a negligent or an intentional misconduct and/or significant deviation to the protocol of the Investigator or the clinical investigational site or the subjects. The Sponsor has taken out insurance to cover any bodily injury and property damage caused by the operations carried out by the insured.

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APPENDIX A SCHEDULE OF EVENTS

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3 Discharge/ Early termination	Day 4 to 6 Safety Follow-Up
Informed consent	•					
Information on the risks of smoking/advice on smoking cessation and debriefing on Nicotine pouch 1.0	•	•			• [p]	
Inclusion/exclusion criteria [a]	•	•				
Nicotine/Tobacco product use history	•	•				
Demographics [b]	•					
Medical history, concomitant diseases	•	•[c]	•[c]	•[c]	•[c]	
Prior medication/ Concomitant medication [d]	•	•	•	•	• [p]	• [q]
Physical examination	•	•			• [p]	
Body height, weight and related BMI	•					
Vital signs [e]	•	•	•	•	• [p]	

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3 Discharge/ Early termination	Day 4 to 6 Safety Follow-Up
ECG [f]	•	•			• [p]	
Spirometry	•					
Blood and urine sample for hematology, clinical chemistry, urine analysis safety panel [g]	•	•			• [p]	
Blood sample for serology [h]	•					
Urine sample for drug test	•	•				
Urine sample for cotinine test	•	•				
Urine pregnancy test (females)	•	•			• [p]	
Blood sample for *trans*-3'-hydroxycotinine and cotinine (CYP2A6 activity) in plasma [i]		•				
Fagerström Test for Nicotine Dependence	•					
NP-1 product test [j]		•				
Enrollment		•				
Randomization		•				
30 min product use periods in the morning and in the afternoon			•	•	•	
Blood sample collection for plasma nicotine [l]			•	•	•	

Study Day	Day -22 to -2 Screening	Day -1 Admission	Day 1	Day 2	Day 3 Discharge/ Early termination	Day 4 to 6 Safety Follow-Up
Product Evaluation Scale (PES) [m]			●	●	●	
VAS craving assessment [n]			●	●	●	
VAS liking (in-the-moment) assessment [n]			●	●	●	
VAS liking (overall) assessment [n]			●	●	●	
VAS satisfaction assessment [n]			●	●	●	
VAS intention-to-use-again assessment [n]			●	●	●	
Sensory questionnaire [m]			●	●	●	
AE/SAE recording	●	●	●	●	● [p]	●
Product events		●	●	●	● [p]	
Support during periods of abstinence from any tobacco and nicotine containing products (as required)		●	●	●	●	
Collection of used products [o]			●	●	●	

Abbreviations: AE = Adverse event; BMI = Body mass index; ECG = Electrocardiogram; SAE = Serious adverse event

a. Prior to enrollment at Admission on Day -1, the following inclusion and exclusion criteria will be re-checked: Inclusion Criteria: (4) Subject 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), (5) Subject does not plan to quit smoking or using other nicotine/tobacco-containing products in the next 3 months. Exclusion criteria: (10) Subject has a positive urine drug including alcohol test, (15) For women only: subject is pregnant (does not have negative pregnancy tests at Screening Visit and at Admission) or is breastfeeding, (16) For women of childbearing potential only: subject does not agree to use an acceptable method of effective contraception, (17) Use of estrogen-containing hormonal contraception or hormone replacement therapy.

The following eligibility criteria will only be checked at Admission: (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.

b. Sex, date of birth/age, race and ethnicity.

c. Concomitant disease status.

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

e. Systolic and diastolic blood pressure, pulse rate and respiratory rate. On Day 1 to Day 3 in the morning, vital signs will be assessed prior to T_{0M}.

f. At Screening an ECG will be performed after signed ICF and at least 1 hour after smoking cigarettes, on Day -1 an ECG will be performed prior to enrollment, on Day 3 an ECG will be performed 60 minutes ± 10 minutes after T_0.

g. Blood samples should be taken in the morning of the Screening visit, Admission (Day -1) and Discharge (Day 3) or at Early termination. Subjects should have fasted for at least 10 hours prior to safety laboratory assessments except at the Screening visit and Early termination where non-fasting samples will be used.

h. Tests for hepatitis B (HbsAg), hepatitis C (HCV antibody) virus and human immunodeficiency virus (anti-HIV1/2) will be performed at the Screening Visit.

i. Sample taken prior to NP-1 product test.

j. On Day -1, after enrollment, subjects will perform a product test using NP-1 for 30 minutes (± 1 minute).

k. On Day 1 to Day 3 in the morning and in the afternoon, subjects will use one product for 30 minutes (± 1 minute) according to the randomized product use sequence.

l. On Day 1 to Day 3, 24 blood samples will be taken for determination of nicotine concentration: one blood sample will be taken prior to the start of product use in the morning (T_{0A}) 5 minutes ± 1 minute (T-1). Thereafter in relation to T_{0A}, blood will be drawn at the following time points: 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.
On Day 2, 2 additional blood samples will be taken for determination of the terminal elimination half-life ($t_{1/2z}$). Blood samples will be taken in relation to T_{0A} from Day 2 at the following time points: T1z after 8 hours ± 5 minutes and T2z after 12 hours ± 5 minutes.

m. On Day 1 to Day 3 in the morning and in the afternoon, the PES and the Sensory questionnaire will be answered at T9 after 1 hour ± 5 minutes, after T_{0M} and T_{0A}.

n. On Day 1 to Day 3 in the morning and in the afternoon, VAS craving, VAS liking (in the moment) and VAS satisfaction assessments at: Within 15 minutes prior to T_{0M} and T_{0A} (VAS craving only), and at 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}. On Day 1 to Day 3 in the morning and in the afternoon, VAS liking (overall) assessment at: T10 after 3 hours ± 5 minutes, after T_{0M} and T_{0A}. On Day 1 to Day 3 in the morning and in the afternoon, VAS intention to use again assessment at: T6 after 30 minutes ± 1 minute, and T10 after 3 hours ± 5 minutes, after T_{0M} and T_{0A}.

o. On Day 1 to Day 3 in the morning and in the afternoon, used product will be collected for analysis of residual nicotine.

p. Early termination assessments to be conducted in subjects who withdraw consent / are discontinued from the study.

q. Only medication administered as treatment for an adverse event

Confidentiality Statement

APPENDIX B PARTICIPATING LABORATORIES

Bioanalytical laboratory (Plasma Nicotine and CYP2A6 analyses):

[redacted]

Safety Laboratory:

[redacted]

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Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 07-Mar-2022 15:50:24 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: A Date of signature: 07-Mar-2022 15:51:18 GMT+0000

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