Clinical study protocol	
Investigational products	Nicotine pouches
Study code	SM26-01
Protocol version and date	Final v1.1; 17FEB2026

Pharmacokinetics and pharmacodynamics of nicotine pouches following controlled single-dose administration in daily nicotine pouch users

Investigational products and dose

Nicotine pouch (NP)1 – Smooth 1.5 mg
NP2 – Wintergreen 1.5 mg
NP3 – Smooth 3 mg

Sponsor signatory

[redacted]

Swedish Match North Europe AB
Maria Skolgata 83
SE-118 53 Stockholm, Sweden

[redacted]

Coordinating Investigator

Björn Schultze, MD

Clinical Trial Consultants AB

Clinical study conduct

CTC Clinical Trial Consultants AB

CTC Uppsala
Dag Hammarskjölds väg 10C
SE-752 37 Uppsala, Sweden

CTC EbbePark
Ebbegatan 3
SE-582 13 Linköping, Sweden

Clinical study management

CTC Clinical Trial Consultants AB
Dag Hammarskjölds väg 10B
SE-752 37 Uppsala, Sweden

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DOCUMENT HISTORY

The following changes have been made to the first regulatory authorized version of this document (version 1.0; 18DEC2025).

Type of change	Summary of changes	Revised protocol version
Minor corrections	Removal of "tobacco products" from IP description on page 1. The study only includes nicotine pouches.	Final v1.1; 17FEB2026
	Correction of minor errors.	

IP=investigational product.

1 STUDY SYNOPSIS

Study title Pharmacokinetics and pharmacodynamics of nicotine pouches following controlled single-dose administration in daily nicotine pouch users	
Study code SM26-01	**Planned study period** Q1 2026 to Q2 2026
Coordinating/Principal Investigator Björn Schultze, MD CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden	
Study design This is a multi-center, open-label, randomized, three-way crossover, single-dose administration study designed to assess nicotine exposure from NP products. The investigational products (IPs) include two unflavored NP products (Smooth, 1.5 mg and 3 mg) and one flavored NP product (Wintergreen, 1.5 mg).	
Objectives Primary objective To assess the similarity in baseline-adjusted $AUC_{0\text{-}inf}$ between the unflavored NP1 product (Smooth, 1.5 mg) and the flavored NP2 product (Wintergreen, 1.5 mg) following single-dose administrations. Secondary objectives 1. To describe the differences in *in vivo* extracted amounts (mg/unit) and extracted fractions (%) of nicotine among the three NP products following single-dose administration. 2. To compare the pharmacokinetic (PK) profiles between the three NP products following single-dose administrations. 3. To assess the similarity in baseline-adjusted C_{max} between the unflavored NP1 product (Smooth, 1.5 mg) and the flavored NP2 product (Wintergreen, 1.5 mg) following single-dose administration. 4. To assess the pharmacodynamic (PD) effects, measured as pulse rate and subjective outcome measures, of the three NP products following single-dose administration. 5. To assess the safety and tolerability of the three NP products following single-dose administration in current, daily NP users. Exploratory objectives 1. [redacted] 2. To assess nicotine extraction-normalized PK profiles among the three NP products following single-dose administration.	

Endpoints

Primary endpoint

Similarity between NP1 and NP2 based on the geometric least squares means (LSMeans) ratio of baseline-adjusted $AUC_{0\ inf}$ within the range of 0.8 to 1.25.

Secondary endpoints

1. *In vivo* extracted amounts (mg/unit) and extracted fractions (%) of nicotine for each of the three NP products.
2. Non-adjusted and baseline-adjusted PK parameters $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}1.5h}$, C_{max}, T_{max}, and $T_{1/2}$ for each of the three NP products.
3. Similarity between NP1 and NP2 based on the geometric LSMeans ratio of baseline-adjusted C_{max} within the range of 0.8 to 1.25.
4. a) The pulse rate parameters E_{imax}, T_{Eimax}, $E_{max0\text{-}60}$, and $T_{Emax0\text{-}60}$, measured using a pulse oximeter, for each of the three NP products.

   b) The subjective "craving" parameters E_{dmax} and T_{Edmax}, measured through a 100 mm visual analog scale (VAS), for each of the three NP products.

   c) The subjective "satisfaction" parameters E_{vmax} and T_{Evmax}, measured through a 100 mm VAS, for each of the three NP products.

   d) The subjective outcome parameters "product liking", and "intent to use again", measured through a 100 mm VAS, for each of the three NP products.
5. Frequency, intensity, and seriousness of adverse events (AEs).

Exploratory endpoints

1. [redacted]
2. Nicotine extraction-normalized $AUC_{0\text{-}inf}$ and C_{max} for each of the three NP products.

Number of subjects planned

Approximately 67 subjects are planned to be screened to achieve 42 randomized subjects and at least 36 evaluable subjects.

An effort will be made to randomize at least 40% of subjects from the least represented sex, corresponding to about 14 subjects. However, a minimum of 20% (about seven subjects) will be considered acceptable.

Diagnosis and main eligibility criteria

Healthy male and female subjects aged ≥21 to ≤60 years who have used NP products for ≥1 year, with a minimum daily consumption of five pouches. All subjects must be willing to comply with study procedures and provide written informed consent.

Subjects will be excluded from the study if they are pregnant, breastfeeding, or intend to become pregnant during the study. Subjects with a history or presence of diagnosed hypertension or cardiovascular disease will also be excluded. The same applies to subject with any other medical condition that may interfere with the evaluation of the IPs or may put the subject at risk because of participation in the study. Subjects intending to stop using nicotine-containing products will also be excluded from the study.

Methodology

Subjects will report to a study site for a screening visit (Visit 1) followed by three IP use visits (Visits 2 to 4) held on separate days. At each IP use visit, subjects will receive IP in a randomized crossover fashion, with 30 minutes of IP use per occasion.

The screening visit (Visit 1) will take place within 4 weeks prior to Visit 2 (-28 days) and will include an eligibility check, including evaluation of prior nicotine use, collection of medical history, a brief physical examination, serology tests, electrocardiogram (ECG), vital signs (pulse rate and blood pressure), height, weight, and body mass index (BMI) assessments.

Subjects will return to the study site for each IP use visit, starting with Visit 2. Eligibility confirmation and randomization will occur before the first IP use at Visit 2. At Visit 2, subjects will also undergo drug and alcohol screening as well as pregnancy testing for female subjects of childbearing potential.

Subjects shall abstain from all nicotine products for 12 hours before each IP use visit (Visits 2 to 4). All IP use sessions will be performed during the morning hours (08:00 to 12:00) to facilitate abstinence. The IPs will be administered as single pouches in a pre-determined randomized order.

During IP use sessions at Visits 2 to 4, subjects will keep the pouch between their upper lip and gum for 30 minutes. Subjects will be instructed not to manipulate the pouch with the tongue or lips, and to refrain from drinking, chewing gum, or brushing their teeth for 30 minutes before use, during use, and for 30 minutes after IP removal.

Blood samples for the determination of nicotine plasma levels and subsequent calculation of PK parameters will be collected pre use (within -10 minutes to -1 minute prior to start of IP use), and at 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 60 minutes, 1 hour:30 minutes, 2 hours, 4 hours, and 6 hours post use.

PD effects will be assessed by measuring pulse rate using a pulse oximeter, as well as subjective outcome parameters through VAS questions and an MCQ, at pre-determined time points. Pulse rate will be measured at pre use (-15 minutes prior to start of IP use), and at the same post-use timepoints as PK sampling (within -1 minute prior to each PK blood sampling, if possible).

Subjective outcome parameters will include “craving”, “satisfaction”, “product liking”, and “intent to use again”. “Craving” and “satisfaction” will be assessed at the same post-use timepoints as PK sampling (“craving” baseline will be assessed -10 minutes prior to start of IP use). “Product liking” and “intent to use again” will be assessed at the 30 minute timepoint. [redacted]

Used pouches will be collected after 30 minutes of use and frozen and -20°C pending determination of residual nicotine in the IPs. The extracted amount (mg/unit) and extracted fraction (%) of nicotine will be assessed. Unused pouches from the same batches (kept by the extraction analysis laboratory) will serve as references and will be stored at -20°C pending analysis.

AEs will be collected through subject interviews and will also include any AEs reported spontaneously by the subjects, beginning from the start of IP use at Visit 2 until the end of Visit 4. Any uses of prior and concomitant medications will also be recorded.

Visits 3 and 4 will follow the same schedule as Visit 2, excluding certain study site admission procedures as described above. Each IP use visit will be scheduled on separate days, preferably with at least 24 hours between visits. Visits on consecutive days are acceptable, provided that not all IP use visits occur consecutively.

The date of each subject’s final IP use visit (Visit 4) will be considered the subject’s end of study date.

Investigational products and dose

- NP1 – Smooth 1.5 mg
- NP2 – Wintergreen 1.5 mg
- NP3 – Smooth 3 mg

Duration of investigational product use

The participating subjects will receive IPs on three occasions, in a randomized crossover fashion, with 30 minutes of IP use per occasion.

Duration of each subject's involvement in the study

Each subject will participate in the study for a period of approximately two weeks, not including the preceding four-week screening period.

Pharmacokinetic assessments

Blood sampling for the determination of nicotine plasma concentrations and subsequent calculation of PK parameters.

Pharmacodynamic assessments

Pulse rate measurement using a pulse oximeter. Subjective outcome parameters measured through VAS questions and an MCQ.

Nicotine extraction assessment

The extracted amount (mg/unit) and extracted fraction (%) of nicotine will be assessed in used pouches.

Safety assessments

AE reporting. Reporting of prior and concomitant medication use.

Statistical methods

Determination of sample size

The sample size was calculated assuming a 2 × 2 crossover design analyzed on a log scale, and is based on the primary endpoint comparison to assess similarity in $AUC_{0\text{-}inf}$ between NP1 (Smooth, 1.5 mg) and NP2 (Wintergreen, 1.5 mg).

Parameters assumed in the power calculation, solving for sample size, are the following:

- Power: 80%.
- Alpha: 5%. Two one-sided tests of alpha = 5% are used.
- Hypothesized true geometric least square means ratio: 1.
- Similarity bounds for the geometric LSMeans ratio: 0.8 to 1.25.
- Coefficient of variation (CV): 0.325, as observed in previous studies.
- Assumed drop-out rate: ~14%.
- Total sample size: 42 subjects randomized to achieve 36 evaluable subjects for the primary endpoint.

General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value, Q1-Q3 (interquartile range [IQR]). In addition, for the parameters AUC and C_{max}, the geometric mean and CV will be presented.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by IP, and by assessment time. Individual subject data will be listed by subject number, IP, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using the SAS Version 9.4 or later (SAS Institute, Inc., Cary NC, United States [US]). The PK parameters will be calculated using non-compartmental analysis with the Phoenix WinNonlin® software version 8.6 or later (Certara Inc., Princeton NJ, US).

Baseline will be defined as the last non-missing data collection time point prior to each IP use.

No adjustment for multiple comparisons will be made. All significant findings will be reviewed for clinical relevance.

Generally, no imputation of data will be performed. In case of missing start and stop times of AEs that cannot be investigated further, missing data will be imputed according to a worst-case scenario, *i.e.*, the start time will be imputed as the closest time point post IP administration and end time as 23:59, resulting in the longest possible treatment-emergent duration of the AE.

PK plasma concentrations below the lower limit of quantification (LLOQ) will be imputed according to pre-determined methods when calculating descriptive statistics and PK parameters.

Spurious data will be continuously evaluated through data validation. If associated with protocol deviations, such data will be assessed on a case-by-case basis prior to the declaration of clean file and database lock, at the latest.

Deviations from the original statistical analysis plan (SAP) will be described in the clinical study report (CSR).

The handling of missing, unused, and spurious data may be further detailed in the SAP.

Study reporting

After completion of the study, an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 guideline-compliant CSR will be prepared.

2 TABLE OF CONTENTS

2.1 List of tables

2.2 List of figures

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration *vs.* time curve
$AUC_{0\text{-inf}}$	AUC from time 0 extrapolated to infinity
$AUC_{0\text{-last}}$	AUC from time 0 to the time of the last measurable plasma concentration
$AUC_{0\text{-}1.5h}$	AUC from time 0 to 1.5 hours post use
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum observed concentration
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
CTC	CTC Clinical Trial Consultants AB
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
E_{dmax}	Largest decrease from baseline
E_{imax}	Highest increase from baseline
E_{max}	Maximum effect
$E_{max0\text{-}60}$	E_{max} from 0 to 60 minutes
EU	European Union
E_{vmax}	Largest value
FAS	Full analysis set
GCP	Good clinical practice
GDPR	General data protection regulation
HIV	Human immunodeficiency virus
ICF	Informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IP	Investigational product
ISF	Investigator site file
IQR	Interquartile range
$Lamda_z$	The estimated terminal elimination rate constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LLOQ	Lower limit of quantification
LSMeans	Least squares means
MCQ	Multiple-choice question
MedDRA	Medical dictionary for regulatory activities
NP	Nicotine pouch
PD	Pharmacodynamics
PK	Pharmacokinetics
PKAS	PK analysis set
PQ/PR interval	The time from the onset of the P wave to the start of the QRS complex (ECG parameter)
PT	Preferred term
QRS interval	The time required for stimulus to spread through the heart's ventricles (ECG parameter)
QT interval	The time from the beginning of the QRS complex to the end of the T wave (ECG parameter)
QTcF	Corrected QT interval by Fredericia (ECG parameter)
QTL	Quality tolerance limits
RBM	Risk-based monitoring
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SOC	System organ class
SOP	Standard operating procedures
$T_{1/2}$	Terminal elimination half-life
T_{Edmax}	Time to reach E_{dmax}
T_{Eimax}	Time to reach E_{imax}

Abbreviation	Definition
T_{Emax}	Time to reach E_{max}
$T_{Emax0-60}$	Time to reach $E_{max0-60}$
T_{Evmax}	Time to reach E_{vmax}
T_{max}	Time of occurrence of C_{max}
TMF	Trial master file
US	United States (of America)
VAS	Visual Analog Scale
WHO	World Health Organization

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 Medical emergencies contact

The Principal Investigator at each study site is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are described in Section 11.4.4.11.

In the case of a medical emergency, the Investigator may, during office hours, contact the Sponsor's medically responsible person (Table 4.1-1).

Table 4.1-1 Medical emergencies contact

Name	Function in the study	Contact information
[redacted]	[redacted]	[redacted]

5 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor

Swedish Match North Europe AB
Maria Skolgata 83
SE-118 53 Stockholm, Sweden

Sponsor's medical representative

[redacted]

Sponsor's project manager

[redacted]

Clinical conduct, Site 1

Clinical Trial Consultants AB

CTC Uppsala
Dag Hammarskjölds väg 10C
SE-752 37 Uppsala, Sweden

Coordinating Investigator/Principal Investigator, Site 1

Björn Schultze, MD
Phone: +46 (0)76 127 31 78
E-mail: bjorn.schultze@ctc-ab.se

Clinical conduct, Site 2

CTC EbbePark
Ebbegatan 3
SE-582 13 Linköping, Sweden

Principal Investigator, Site 2

Anne-Marie Landtblom, MD, PhD
Phone: +46 (0)70 559 16 70
E-mail: anne-marie.landtblom@ctc-ab.se

Study management

Clinical Trial Consultants AB
Dag Hammarskjölds väg 10B
SE-752 37 Uppsala, Sweden

Clinical research manager

[redacted]

Biostatistician

[redacted]

Pharmacokineticist

[redacted]

Medical writer (author of the clinical study protocol [CSP])

[redacted]

Laboratory (virology)

Synlab Sverige AB
Nytorpsvägen 28–32
SE-183 53 Täby, Sweden

Laboratory (bioanalysis)	Lablytica Life Science AB Virdings Allé 16 SE-754 50 Uppsala, Sweden
Laboratory (extraction)	Regulatory & Scientific Affairs Swedish Match North Europe AB Maria Skolgata 83 SE-118 53 Stockholm, Sweden
Investigational product (IP) manufacturing	[redacted]
IP packaging and labeling	Regulatory & Scientific Affairs Swedish Match North Europe AB Maria Skolgata 83 SE-118 53 Stockholm, Sweden
Electronic data capture (EDC) system provider	Viedoc Technologies AB Stationsgatan 23 SE-753 40 Uppsala, Sweden

Signatures are provided in Section 19.

6 INTRODUCTION

6.1 Background

Tobacco harm reduction involves adopting strategies to minimize the health risks associated with tobacco use, particularly for individuals who do not wish to quit nicotine usage [1]. This approach includes transitioning from more harmful combustible cigarettes to potentially less harmful alternatives such as Swedish snus and nicotine pouches (NPs), providing viable options for nicotine delivery with potentially reduced health risks.

The use of oral tobacco (*e.g.*, Swedish snus, moist snuff) is by definition unassociated with exposure to the many thousands of combustion compounds found in tobacco smoke (many of which are highly carcinogenic and may induce a state of systemic, chronic inflammation), or chronic irritation in the upper and lower airways resulting from the inhalation of tobacco smoke. Therefore, it is generally accepted that the use of oral tobacco products has substantially lower health risks than cigarette smoking.

Nicotine is addictive and contributes to the addictive properties of tobacco products. Nicotine is not risk free, but is not the primary cause of smoking-related diseases. Additionally, oral tobacco products typically contain low levels of unwanted substances, including nitrosamines and polycyclic hydrocarbons, which have been classified as human carcinogens. While the health effects of oral tobacco are substantially smaller compared to cigarette smoking, some potential adverse effects cannot be ruled out, particularly those related to nicotine exposure.

NP products have been commercially available since they were first launched in the United States (US) in 2014. They share some features with snus, as they come in pouches intended to be placed under the upper lip. However, unlike snus, these products contain no nitrosamines or polycyclic hydrocarbons. The nicotine content in NP is comparable to that in snus and moist snuff which are commonly used in Scandinavia and the US, with levels typically up to 20 mg/unit, but sometimes higher.

When comparing the nicotine content of different nicotine-delivery products, it is important to consider that nicotine extraction and uptake vary considerably depending on product type (tobacco *vs*. non-tobacco-based matrix) and product formulation (pouch geometry, solubility, water content, particle size, pH, *etc*.). Additionally, there is substantial inter-individual variation in uptake for products used orally, likely related to constitutional differences in saliva production, resulting in a wide variation in nicotine extraction.

Flavor compounds in NP products may influence subjective experiences such as taste, satisfaction and craving relief. These factors can affect product acceptability and use patterns, which may indirectly impact nicotine exposure and user safety.

6.2 Study rationale

This study aims to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of NP products under controlled conditions to assess nicotine exposure and user safety. Assessing the similarity in baseline-adjusted $AUC_{0\text{-}inf}$ between the unflavored NP1 product (Smooth, 1.5 mg) and the flavored NP2 product (Wintergreen, 1.5 mg) is critical to determine whether flavoring significantly alters systemic nicotine exposure.

Secondary objectives of the study address complementary aspects of product evaluation:

- Nicotine extraction provides insight into the amounts of nicotine subjects are exposed to, which can vary considerably between individuals, and into the product's efficiency.

- PK profile comparisons across all three NP products help identify differences in absorption and exposure.
- PD assessments (pulse rate and subjective measures) evaluate physiological and behavioral responses, supporting a comprehensive safety profile.
- Safety and tolerability evaluation ensures that single-dose administration in daily NP users does not pose undue risk.

Together, these objectives provide a comprehensive understanding of nicotine uptake, user experience, and safety, which are essential for regulatory compliance and informed product development.

The rationale for the study design is presented in Section 8.3.

6.3 Risk-benefit assessment

6.3.1 Risk assessment

All research subjects must be daily NP users for at least 1 year, with a minimum daily consumption of five pouches. Consequently, the subjects are well acquainted with and accustomed to the effects of nicotine, minimizing the risk of developing any new nicotine dependency.

The study will involve single-dose administration of three different NP products: two unflavored products (1.5 mg and 3 mg), and one flavored product (1.5 mg). While products with higher nicotine content are commercially available, subjects must abstain from all nicotine products for at least 12 hours before each IP use visit and will receive only one product per visit. Therefore, overall daily nicotine exposure is expected to be lower than usual during study visits.

Subjects who intend to change their nicotine consumption habit or stop using nicotine-containing products, and/or are pregnant, breastfeeding, or intend to become pregnant during the study, and/or subjects with a history or presence of diagnosed hypertension, cardiovascular disease or other medical condition who may be particularly vulnerable to nicotine exposure, will be excluded from participation.

The nicotine in the NP products is of pharmaceutical grade, the same as the nicotine used in nicotine replacement products (*e.g.*, gum, lozenges, mouth spray, *etc*.). Except for nicotine, all ingredients contained in the NP products are food grade and approved for use in food in Sweden, and classified as Generally Recognized as Safe (GRAS) by the US Food and Drug Administration (FDA).

The potential adverse effects of the study procedures are expected to be minor and clinically insignificant, based on experience from clinical studies on similar products [2-9]. Notably, previous clinical studies with similar products have reported no adverse events (AEs) other than those likely attributed to nicotine exposure, such as salivation, nausea, and dyspepsia.

The Principal Investigator at each study site will ascertain that adequate facilities and procedures are available to handle emergency situations should they occur during the study. The medical staff at the study sites have extensive experience in clinical studies, and there are adequate procedures in place to handle unexpected and expected adverse experiences in the study subjects.

Aside from the risks related to the IPs, as detailed above, there may also be risks related to the medical devices used in the study (*e.g.*, venipuncture or indwelling venous catheters). However, these devices are used in routine medical care and the risk associated with their use is considered low and ethically justifiable. Repeated blood sampling for PK analysis will occur on separate days, with at least 24 hours between visits to allow sufficient time between sampling sessions. Study-specific evaluations and sampling procedures, such as blood pressure measurements using a blood pressure cuff (at screening) and frequent blood sampling (during Visits 2 to 4), may cause transient discomfort. However, the risk is deemed to be low and ethically justifiable.

6.3.2 Benefit assessment

Analogous to regular phase I clinical studies in healthy volunteers, there is no direct benefit for the subjects to participate in the study, aside from a brief medical examination, which may provide them with information on their general state of health.

6.3.3 Risk/benefit conclusion

Safety data from previous pre-clinical and clinical studies have not identified concerns that outweigh the anticipated scientific benefits of this study. Potential AEs and risks associated with the study procedures are expected to be minor and clinically insignificant. Therefore, the planned assessments and risk mitigation strategies are considered sufficient to achieve the study's objectives while ensuring that subjects are not exposed to ethically unjustifiable risks.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary objectives and endpoints

The primary study objective and endpoint are presented in Table 7.1-1 below.

Table 7.1-1 Primary study objective and endpoint

Primary objective	Primary endpoint	Assessment	Analysis
To assess the similarity in baseline-adjusted $AUC_{0\text{-inf}}$ between the unflavored NP1 product (Smooth, 1.5 mg) and the flavored NP2 product (Wintergreen, 1.5 mg) following single-dose administration.	Similarity between NP1 and NP2 based on the geometric LSMeans ratio of baseline-adjusted $AUC_{0\text{-inf}}$ within the range of 0.8 to 1.25.	Blood sampling for nicotine plasma concentration and PK analysis (Section 11.3.1).	Section 17.7.1.

CI=confidence interval, LSMeans=least squares means, NP=nicotine pouch, PK=pharmacokinetic. For the definition of pharmacokinetic (PK) parameters, refer to Section 17.8.2 or the list of abbreviations and terms in Section 3.

7.2 Secondary objective and endpoints

Secondary study objectives and endpoints are presented in Table 7.2-1 below.

Table 7.2-1 Secondary objectives and endpoints

Secondary objectives	Secondary endpoints	Assessments	Analysis
1. To describe the differences in *in vivo* extracted amounts (mg/unit) and extracted fractions (%) of nicotine among the three NP products following single-dose administration.	1. *In vivo* extracted amounts (mg/unit) and extracted fractions (%) of nicotine for each of the three NP products.	Determination of nicotine extracted from pouches (Section 11.4.1).	Section 17.8.1.
2. To compare the PK profiles between the three NP products following single-dose administration.	2. Non-adjusted and baseline-adjusted PK parameters $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-1.5h}}$, C_{max}, T_{max}, and $T_{1/2}$ for each of the three NP products.	PK sampling and analysis related to secondary endpoints (Section 11.4.2).	Section 17.8.2.
3. To assess the similarity in baseline-adjusted C_{max} between the unflavored NP1 product (Smooth, 1.5 mg) and the flavored NP2 product (Wintergreen, 1.5 mg) following single-dose administration.	3. Similarity between NP1 and NP2 based on the geometric LSMeans ratio of baseline-adjusted C_{max} within the range of 0.8 to 1.25.	PK sampling and analysis related to secondary endpoints (Section 11.4.2).	Section 17.8.3.
4. To assess the PD effects, measured as pulse rate and subjective outcome measures, of the three NP products following single-dose administration.	4a. The pulse rate parameters E_{imax}, T_{Eimax}, $E_{max0\text{-}60}$, and $T_{Emax0\text{-}60}$, measured using a pulse oximeter, for each of the three NP products.	Pulse rate evaluation (Section 11.4.3.1).	Section 17.8.4.
	4b. The subjective "craving" parameters E_{dmax} and T_{Edmax}, measured through a 100 mm visual analog scale (VAS), for each of the three NP products.	Subjective outcomes evaluation (Section 11.4.3.2).	Section 17.8.4.

Secondary objectives	Secondary endpoints	Assessments	Analysis
	4c. The subjective "satisfaction" parameters E_{vmax} and T_{Evmax}, measured through a 100 mm VAS, for each of the three NP products.	Subjective outcomes evaluation (Section 11.4.3.2).	Section 17.8.4.
	4d. The subjective outcome parameters "product liking" and "intent to use again", measured through a 100 mm VAS, for each of the three products.	Subjective outcomes evaluation (Section 11.4.3.2).	Section 17.8.4.
5. To assess the safety and tolerability of the three NP products following single-dose administration in current, daily NP users.	5. Frequency, intensity, and seriousness of adverse events (AEs).	AE reporting (Section 11.4.4).	Section 17.8.5.

LSMeans=least squares means, NP=nicotine pouch, PD=pharmacodynamic, PK=pharmacokinetic, VAS=visual analog scale. For the definition of PK parameters and PD variables, refer to Section 17.8.2 (PK), Section 17.8.4 (PD) or the list of abbreviations and terms in Section 3.

7.3 Exploratory objectives and endpoints

Exploratory objectives and endpoints are presented in Table 7.3-1 below.

Table 7.3-1 Exploratory objectives and endpoints

Exploratory objectives	Endpoints	Assessments	Analysis
1. [redacted]	1. [redacted]	Subjective outcomes evaluation (Section 11.5.1).	Section 17.9.1.
2. To assess nicotine extraction-normalized PK profiles among the three NP products following single-dose administration.	2. Nicotine extraction-normalized $AUC_{0\text{-}inf}$ and C_{max} for each of the three NP products.	Nicotine extraction-normalized PK parameters (Section 11.5.2).	Section 17.9.2.

NP=nicotine pouch, PK=pharmacokinetic. For the definition of PK parameters, refer to Section 17.8.2 or the list of abbreviations and terms in Section 3.

8 STUDY DESIGN

8.1 Overall study design

This is a multi-center, open-label, randomized, three-way crossover, single-dose administration study in healthy male and female volunteers. The IPs include two unflavored NP products (Smooth, 1.5 mg and 3 mg) and one flavored NP product (Wintergreen, 1.5 mg).

Subjects will report to a study site for a screening visit (Visit 1), followed by three IP use visits (Visits 2 to 4) held on separate days. At each IP use visit, subjects will receive IP in a randomized crossover fashion, with 30 minutes of IP use per occasion.

Forty-two (42) subjects will be randomized to achieve at least 36 evaluable subjects. Refer to Section 17.3 for the sample size calculation and definition of evaluable subjects.

The subjects will be healthy male and female subjects aged ≥21 to ≤60 years who have used NP products for ≥1 year, with a minimum daily consumption of five pouches. Efforts will be made to randomize at least 40% of subjects from the least represented sex, with a minimum of 20% considered acceptable.

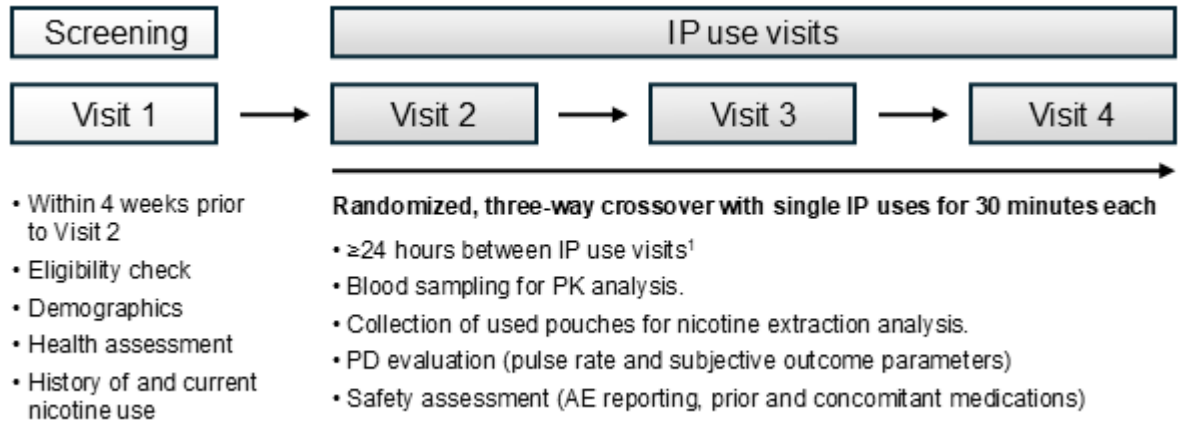
Each subject will participate in the study for a period of approximately two weeks, not including the preceding up-to four-week screening period.

An overview of the study design is shown in Figure 8.1-1 below.

The overall schedule of events is presented in Table 8.2-1 and the detailed schedule of events for the IP use visits is presented in Table 8.2-2.

Study assessments are described in Section 11.

Figure 8.1-1 Overview of the study design



AE=adverse event, IP=investigational product, PD=pharmacodynamic, PK=pharmacokinetic.

1. Each IP use visit will be scheduled on a separate day, preferably with at least 24 hours between visits. Visits on consecutive days are acceptable, provided that not all IP use visits take place consecutively.

8.2 Detailed schedule of events

The screening visit (Visit 1) will take place within 4 weeks prior to Visit 2 (-28 days) and will include an eligibility check, including evaluation of prior nicotine use, collection of medical history, a brief physical examination, serology tests, electrocardiogram (ECG), vital signs (pulse rate and blood pressure), height, weight, and body mass index (BMI) assessments (see Table 8.2-1).

Subjects will return to the study site for each IP use visit, starting with Visit 2. Eligibility confirmation and randomization will occur before the first IP use at Visit 2. At Visit 2, subjects will also undergo drug and alcohol screening as well as pregnancy testing for female subjects of childbearing potential.

Subjects shall abstain from all nicotine products for 12 hours before each IP use visit (Visits 2 to 4). All IP use sessions will be performed during the morning hours (08:00 to 12:00) to facilitate abstinence. The IPs will be administered as single pouches in a pre-determined randomized order (refer to Section 9.9).

During IP use sessions at Visits 2 to 4, subjects will keep the pouch between their upper lip and gum for 30 minutes. Subjects will be instructed not to manipulate the pouch with the tongue or lips, and to refrain from drinking, chewing gum, or brushing their teeth for 30 minutes before use, during use, and for 30 minutes after IP removal.

Blood samples for the determination of nicotine plasma levels and subsequent calculation of PK parameters will be collected pre use (within -10 minutes to -1 minute prior to start of IP use), and at 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 60 minutes, 1 hour:30 minutes, 2 hours, 4 hours, and 6 hours post use (Table 8.2-2).

PD effects will be assessed by measuring pulse rate using a pulse oximeter, and by evaluating subjective outcome parameters through visual analog scale (VAS) questions and a multiple choice question (MCQ), at pre-determined time points. Pulse rate will be measured pre use (-15 minutes prior to start of IP use), and at the same post-use timepoints as PK sampling (within -1 minute prior to each PK blood sampling, if possible).

Subjective outcome parameters will include “craving”, “satisfaction”, “product liking”, and “intent to use again”. “Craving” and “satisfaction” will be assessed at the same post-use timepoints as PK sampling (“craving” baseline will be assessed -10 minutes prior to start of IP use). “Product liking” and “intent to use again” will be assessed at the 30-minute timepoint. [redacted] (Table 8.2-2).

Used pouches will be collected after 30 minutes of use and frozen at -20°C pending determination of residual nicotine in the IPs. The extracted amount (mg/unit) and extracted fraction (%) of nicotine will be assessed. Unused pouches from the same batches (kept by the extraction analysis laboratory; see Section 5) will serve as references and will be stored at -20°C pending analysis.

AEs will be collected through subject interviews and will also include any AEs reported spontaneously by the subjects, beginning from the start of IP use at Visit 2 until the end of Visit 4 (see Table 8.2-1). Any uses of prior and concomitant medications will also be recorded.

Visits 3 and 4 will follow the same schedule as Visit 2, excluding certain study site admission procedures as described above and detailed in Table 8.2-2. Each IP use visit will be scheduled on separate days, preferably with at least 24 hours between visits. Visits on consecutive days are acceptable, provided that not all IP use visits occur consecutively.

The date of each subject’s final IP use visit (Visit 4) will be considered the subject’s end of study date. The overall end of the study will be the date of the final clinical study report (CSR).

Table 8.2-1 Overall schedule of events

Events↓/Visit→	CSP section	Screening[1] Visit 1	IP use visits[2] Visit 2	Visit 3	Visit 4
Informed consent	11.2.1	X			
Demographics	11.2.2	X			
Medical/surgical history	11.2.3	X			
History of and current nicotine use	11.2.4	X			
Inclusion/exclusion criteria	11.2.5	X	X[3]		
Weight, height, and BMI	11.2.6	X			
Physical examination	11.2.7	X			
Vital signs (blood pressure and pulse rate)	11.2.8	X			
Electrocardiogram measurement	11.2.9	X			
HIV, Hepatitis B and C	11.2.10	X			
Pregnancy test[4]	11.2.11	X	X		
Drug screen[5]	11.2.12	X	X		
Alcohol test[5]	11.2.13	X	X		
Randomization	9.9		X		
IP (pouch) administration	10.5		X	X	X
PK blood sampling (plasma)	11.3.1		X	X	X
IP (pouch) collection	11.4.1		X	X	X
Pulse rate (pulse oximeter)	11.4.3.1		X	X	X
VAS questions[6]	11.4.3.2		X	X	X
Multiple-choice question[7]	11.5.1		X	X	X
Baseline symptoms[8]	11.2.14	---------- X ----------			
Adverse event reporting[9]	11.4.4		---------- X ----------		
Prior and concomitant medications	11.2.15	---------- X ----------			

BMI= body mass index, HIV=human immunodeficiency virus, IP=investigational product, MCQ=multiple choice question, PK=pharmacokinetic, VAS=visual analog scale.

1. The screening visit (Visit 1) will take place within 4 weeks prior to Visit 2 (-28 days).
2. Each IP use visit will be scheduled on a separate day, preferably with at least 24 hours between visits. Visits on consecutive days are acceptable, provided that not all IP use visits occur consecutively. The detailed timing of assessments during IP use visits is outlined in Table 8.2-2.
3. Confirmation of eligibility prior to randomization.
4. Only for female subjects of childbearing potential: urine dipstick tests. Additional pregnancy tests may be performed at Visits 3 and 4 at the discretion of the Investigator.
5. Additional drug and alcohol testing may be performed at Visits 3 and 4 at the discretion of the Investigator.
6. Subjective parameters "craving", "satisfaction", "product liking", and "intent to use again".
7. [redacted]
8. Baseline symptoms will be recorded until the first administration of IP at Visit 2.
9. Adverse events will be recorded from the first administration of IP at Visit 2 until the end of Visit 4.

Table 8.2-2 Detailed schedule of events for investigational product use visits (Visits 2 to 4)

Visit→	**Visits 2 to 4**															
Events↓/Time points→	**Admission**	**-00:15**	**-00:10**	**-00:01**	**00:00**	**00:05**	**00:10**	**00:15**	**00:20**	**00:30**	**00:40**	**01:00**	**01:30**	**02:00**	**04:00**	**06:00**
Inclusion/exclusion criteria (Visit 2 only)	X[1]															
Drug screen (Visit 2 only)	X[2]															
Alcohol test (Visit 2 only)	X[2]															
Pregnancy test (Visit 2 only)	X[3]															
Randomization (Visit 2 only)	X															
IP (pouch) administration					X											
IP (pouch) collection										X						
PK blood sampling (plasma)				X[4]		X	X	X	X	X	X	X	X	X	X	X
Pulse rate (pulse oximeter)		X				X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
VAS question (“craving”)			X			X	X	X	X	X	X	X	X	X	X	X
VAS question (“satisfaction”)						X	X	X	X	X	X	X	X	X	X	X
VAS (“product liking” and “intent to use again”)										X						
MCQ [redacted]										X						
Baseline symptoms (Visit 2 only)[6]	---------- X ----------															
Adverse event reporting (Visit 2)[7]					---------- X ----------											
Adverse event reporting (Visits 3 and 4)[7]	---------- X ----------															
Prior and concomitant medications	---------- X ----------															

IP=investigational product, MCQ=multiple choice question, PK=pharmacokinetic, VAS=visual analog scale.

1. Confirmation of eligibility prior to randomization.
2. Additional drug and alcohol testing may be performed at Visits 3 and 4 at the discretion of the Investigator.
3. Only for female subjects of childbearing potential: urine dipstick tests. Additional pregnancy tests may be performed at Visits 3 and 4 at the discretion of the Investigator.
4. The pre-use PK sample may be collected at any time between -10 minutes and -1 minute before the start of IP use, but after the pulse rate assessment at -15 minutes (±5 minutes).
5. Pulse rate (pulse oximetry) measurement should be done within -1 minute prior to each PK blood sampling, if possible.
6. Baseline symptoms will be recorded until the first administration of IP at Visit 2.
7. Adverse events will be recorded from the first administration of IP at Visit 2 until the end of Visit 4.

8.3 Rationale for the study design

This is a multi-center, open-label, randomized, three-way crossover, single-dose administration study designed to assess nicotine exposure from flavored and unflavored NP products, specifically, to determine whether the unflavored NP1 product results in a similar nicotine exposure, measured as $AUC_{0\text{-}inf}$, compared to the flavored NP2 product.

A crossover design was chosen to allow a more efficient evaluation of IPs compared to a parallel study design, as fewer subjects are required because each subject serves as its own control. To minimize carry-over effects, subjects will abstain from all nicotine products for at least 12 hours before each IP use visit.

Randomization will be used to minimize bias in the assignment of subjects to an IP use sequence and to increase the likelihood that known and unknown subject attributes (*e.g.*, demographic and baseline characteristics) are evenly balanced.

9 STUDY POPULATION

Prospective approval of deviations from the eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

9.1 Recruitment

Subjects will be recruited from CTC's database of healthy volunteers, as well as from strategic marketing campaigns. Advertisements in social media and other media (newspapers, internet, radio, local distribution of flyers, *etc.*) will be used to reach the target audience. The advertisement texts approved by the Independent Ethics Committee (IEC) will be used to create all materials (digital, radio and/or print) for recruitment.

9.2 Screening and enrollment log

Investigators must keep a record of all screened subjects even if they were not subsequently included in the study. This information is necessary to verify that subjects were selected without bias. The reason for screening failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects who were included but did not complete the study.

A screening number generated automatically in the electronic case report form (eCRF) will be allocated to each subject in connection with the informed consent process at the screening visit (Visit 1). The screening number will allow the identification of subjects irrespective of their possible eligibility for the study.

Eligible subjects will be assigned a 3-digit randomization number prior to the first IP use. If a subject is unable to receive the planned initial IP use within 28 days after screening (*i.e.*, the time interval between signing informed consent and the first IP use) the subject should undergo re-screening before continuing in the study.

9.3 Number of subjects

Approximately 67 subjects are planned to be screened to achieve 42 randomized subjects and at least 36 evaluable subjects. Refer to Section 17.3 for the sample size calculation and definition of evaluable subjects.

Efforts will be made to randomize at least 40% of subjects from the least represented sex, corresponding to about 14 subjects. However, a minimum of 20% (about seven subjects) will be considered acceptable.

For the replacement of subjects who discontinue the study, see Section 9.8.3.

9.4 Inclusion criteria

For inclusion in the study, the subjects must fulfill the following criteria:

1. Be willing and able to provide written informed consent for participation in the study.
2. Be a user of NP products for ≥1 year, with a minimum daily consumption of five pouches, and be willing and able to use NP products while abstaining from all other nicotine products for at least 12 hours prior to and during Visits 2 to 4. Users of other nicotine products are eligible; however, subjects must primarily be users of NP products to be included.
3. Be a healthy male or female subject aged 21 to 60 years, inclusive.

4. Be medically healthy, without clinically significant abnormalities in medical history, physical examination findings, vital signs, ECG, and/or laboratory results (including hepatitis B/C and human immunodeficiency virus [HIV]) at the time of the screening visit, as judged by the Investigator.
5. Female subjects of childbearing potential must either practice abstinence from heterosexual intercourse (if this reflects their preferred and usual lifestyle) or agree to use a highly effective method of contraception with a failure rate of <1%/year to prevent pregnancy for the duration of the study. Female subjects of childbearing potential with an exclusive male partner who has undergone vasectomy may choose not to use contraceptives.

   Acceptable methods of contraception include:

   - combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal),
   - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), and
   - intrauterine device or intrauterine hormone-releasing system.

9.5 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. A history of diagnosed hypertension or any cardiovascular disease, or current manifestations of either, as judged by the Investigator.
2. Any surgical or medical condition, including abnormal salivation (including pharmaceutically induced), or history thereof, which, in the judgment of the Investigator, might interfere with the absorption, distribution, metabolism, or excretion of the IP or may either put the subject at risk due to study participation, influence the results, or impair the subject's ability to comply with the study.
3. A history of diagnosed severe allergy/hypersensitivity or current manifestations of severe allergy/hypersensitivity to aroma compounds (including fragrances and/or flavorings), as judged by the Investigator.
4. Poor venous access or fear of needles.
5. Any planned major surgery during the study period.
6. Pregnancy, currently breastfeeding, or intention to become pregnant during the course of the study.
7. Positive screening results for serum hepatitis B surface antigen, hepatitis C antibodies, and/or HIV.
8. Positive test results for drugs of abuse or alcohol at screening or upon admission to the study site prior to start of IP use. Positive results consistent with the subject's medical history and prescribed medications may be disregarded, as judged by the Investigator.
9. History of alcohol abuse or excessive alcohol intake, as judged by the Investigator.
10. Presence or history of drug abuse, as judged by the Investigator.
11. History of, or current use of anabolic steroids, as judged by the Investigator.

12. Current, ongoing use of beta-adrenergic blocking agents (beta blockers) or central stimulant medications (psychostimulants), *e.g.*, for the treatment of attention deficit hyperactivity disorder (ADHD), including *pro re nata* (as needed) use, at the discretion of the Investigator.
13. Plasma donation, blood donation or corresponding blood loss within 1 month prior to screening.
14. Intention to change nicotine consumption habits, including plans to stop using nicotine products, within the next 3 months of the screening visit, as judged by the Investigator.
15. The Investigator considers the subject unlikely to comply with study procedures, restrictions, and requirements.

9.6 Restrictions during the study

Subjects must be willing to comply with the restrictions as outlined in Sections 9.6.1 and 9.6.2 below.

9.6.1 General restrictions

1. Contraception requirements: Female subjects of childbearing potential must comply with the contraception requirements outlined in inclusion criterion no. 5 or practice abstinence from heterosexual intercourse, which is only admissible if it reflects their preferred and usual lifestyle.
2. Nicotine products: Subjects must abstain from all nicotine products for at least 12 hours prior to the start of each IP use visit and throughout each IP use visit (Visits 2 to 4).
3. Mouth-related procedures: Subjects must abstain from eating, drinking, or performing any other mouth-related procedure (*e.g.*, tooth brushing) for 30 minutes before IP use, during IP use, and for 30 minutes after IP removal (Visits 2 to 4).
4. Drugs of abuse: Subjects must abstain from any drugs of abuse/recreational drugs throughout the study (Visits 1 to 4).
5. Alcohol: Subjects must abstain from consuming alcohol for at least 12 hours before each IP use visit (Visits 2 to 4).
6. Blood donation: Subjects must not donate plasma or blood from the screening visit (Visit 1) until 1 month after the last IP use visit (Visit 4).
7. Participation in other clinical studies: Subjects are not permitted to participate in any other clinical study during the course of this study (Visits 1 to 4).

9.6.2 Prior and concomitant therapy

Medications known to influence salivation or pulse rate will be prohibited from the screening visit (Visit 1) until the end of Visit 4. This restriction includes, but is not limited to, beta-adrenergic blocking agents (beta blockers) and central stimulants (psychostimulants), including *pro re nata* use. As outlined in exclusion criterion no. 12, subjects currently using beta-adrenergic blocking agents or central stimulants will generally be excluded from participation. Exceptions may be made if the subject is receiving a stable dosing regimen that, in the opinion of the Investigator, is not expected to interfere with the conduct of the study or the interpretation of the results.

No additional restrictions will apply to concomitant medications or therapies, provided that the subject remains on a stable dosing regimen from the screening visit (Visit 1) until the end of Visit 4. However, *pro re nata* medications may be a reason for exclusion, as judged by the Investigator, if they affect the subject's general condition or parameters relevant to the study (*e.g.*, salivation and pulse rate).

As detailed in exclusion criterion no. 8, a positive drug screen will exclude a subject from the study. Positive results that are consistent with the subject's medical history and prescribed medications (*e.g.*, opioid analgesics) may be disregarded as judged by the Investigator.

9.7 Screen failures

Screen failures are defined as subjects who consent to take part in the clinical study but do not fulfill all eligibility criteria and are therefore not included in the study. A minimal set of information must be collected for all screen failures to ensure transparent reporting. This includes documentation of the signed and dated informed consent form (ICF) and reason(s) for screening failure.

Re-screening may be performed if any of the following were reasons for screening failure or non-randomization, as judged by the Investigator:

- Practical reasons.
- Non-significant medical conditions (*e.g.*, influenza, nasopharyngitis).
- Plasma or blood donation outside of the allowed time windows.
- Reserve subject status.

For subjects who are re-screened, a new screening number will be assigned, and a new, signed ICF must be collected.

9.8 Subject withdrawal

9.8.1 General withdrawal criteria

Subjects are free to withdraw from the study at any time and for any reason, without affecting their right to an appropriate follow-up or future medical care. If possible, the reason for withdrawal of consent should be documented.

Subjects may also be withdrawn from the study at any time at the discretion of the Investigator.

Reasons for discontinuation can include:

- AE (as judged by the Investigator and/or Sponsor).
- Death.
- Logistical problem.
- Lost to follow up.
- Non-compliance with study schedule and restrictions.
- Physician decision.
- Pregnancy.
- Protocol deviation.
- Technical problems.
- Withdrawal of consent.

- Other.

9.8.2 Procedures for discontinuation of a subject from the study

A subject who withdraws prematurely from the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. Any ongoing AEs will be followed up as described in Section 11.4.4.12.

The specific primary reason for discontinuation/early withdrawal must be documented in the eCRF, and final drug accountability must be performed. If the reason for discontinuation is an AE, the specific AE must be recorded in the eCRF.

9.8.3 Subject replacement

Subjects who are prematurely withdrawn prior to the start of IP use may be replaced at the discretion of the Sponsor.

9.9 Randomization

At Visit 2, subjects will be randomized to one of six use sequences using a Latin squares William's design, which balances for first-order carry-over effects. The following sequences will be randomized:

Sequence 1: A B C

Sequence 2: B C A

Sequence 3: C A B

Sequence 4: C B A

Sequence 5: A C B

Sequence 6: B A C

where

A = NP1 – Smooth 1.5 mg
B = NP2 – Wintergreen 1.5 mg
C = NP3 – Smooth 3 mg

As this is an open-label study, the IP use sequence assigned to each subject will be recorded in the eCRF. Computer-generated randomization lists for each site will be created using the SAS Proc Plan (SAS Version 9.4). Randomization will be stratified by site. Each randomization list will include site, randomization number, randomization sequence, visit, and product.

The randomization list will be generated by CTC. The original randomization list will be retained by the randomizer, and copies will be provided to each site and to Swedish Match North Europe AB as the IP packing company.

9.10 Blinding,

This is an open-label study; therefore, the Sponsor, Investigators, study staff, and subjects will be aware of the product the subjects receive at all times.

10 INVESTIGATIONAL PRODUCTS

The IPs will be supplied by [redacted]

10.1 Identity of investigational products

The following IPs will be used in the study:

- NP1 – Smooth 1.5 mg
- NP2 – Wintergreen 1.5 mg
- NP3 – Smooth 3 mg

10.2 Manufacturing, packaging, and labeling

All IPs will be manufactured by [redacted] in compliance with applicable laws, including food production laws. Production sites and batch IDs for the IPs will be documented in the trial master file (TMF).

IPs will be transferred from their original container, weighed, and individually packaged into identical sealed food-approved test containers at the Swedish Match North Europe AB analytical laboratory. These containers will be labeled with unique identification numbers according to the randomization lists and shipped by Swedish Match North Europe AB directly to each CTC study site.

10.3 Conditions for storage

At the study sites, IPs will be stored at room temperature (15°C to 25°C) in an access-controlled storage area prior to use. For the storage of used, collected pouches, refer to Section 11.4.1.

10.4 Preparation and accountability

The IPs will be dispensed according to the randomization list by the site personnel. The Investigator will maintain a storage and accountability log, as well as a dispensing log detailing the dates and quantities of study IPs received and used by each subject, along with any IPs destroyed at the end of the study. Products deliberately and/or accidentally destroyed by the site or the subject must be accounted for.

10.5 Investigational product use instructions

A single pouch will be administered in the morning at each IP use visit (Visits 2 to 4). Subjects will keep the pouch between their upper lip and gum for 30 minutes and will be instructed not to manipulate the pouch with their tongue or lips. They will also be instructed not to eat, drink, chew gum, or brush their teeth for 30 minutes before use, during use, and for 30 minutes after removal of the IP.

Subjects must abstain from all nicotine products for at least 12 hours before each IP use visit. To this end, subjects will be instructed to abstain from such products starting at approximately 20:00 (8 pm) the day before IP use visits (Visits 2 to 4). All IP use visits will occur during the morning hours (08:00 to 12:00) to facilitate compliance with abstinence requirements.

10.6 Investigational product final accountability

Any IP not used, as well as all empty containers, will be destroyed at the site upon confirmation from the Sponsor. The Monitor will perform a final IP accountability reconciliation at the end of the study to verify that all unused IP has been properly destroyed and documented.

11 STUDY ASSESSMENTS

The study assessments are described in the sections below and the timing of assessments is detailed in the schedule of events (Table 8.2-1 and Table 8.2-2).

11.1 Recording of data

The Principal Investigators will provide the Sponsor with all data produced during the study from the scheduled assessments. They will ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRF and all required reports.

It is important that IP application and collection of PK blood samples occur as close as possible to the scheduled time points detailed in Table 8.2-2. To achieve this, the timing priority at each time point is:

1. Blood samples for PK.
2. Pulse rate measurement (within -1 minute prior to each PK blood sampling, if possible).
3. VAS questions.
4. MCQ.

Allowed deviations from actual time points are outlined in Table 11.1-1 below.

Table 11.1-1 Allowed deviations from actual time points

Time point	IP use and collection	PK blood sampling (plasma)	Pulse rate (pulse oximetry)	VAS questions "craving" and "satisfaction"	VAS questions "product liking" and "intent to use again"	MCQ [redacted]
-00:15			±5 minutes			
-00:10		*See footnote 3.*		±3 minutes[5]		
-00:01						
00:00	± 0 minutes[1]					
00:05		±2 minutes	±2 minutes[4]	±2 minutes		
00:10		±2 minutes	±2 minutes[4]	±2 minutes		
00:15		±2 minutes	±2 minutes[4]	±3 minutes		
00:20		±2 minutes	±2 minutes[4]	±3 minutes		
00:30	±1 minutes[2]	±5 minutes	±2 minutes[4]	±5 minutes	±10 minutes	±10 minutes
00:40		±5 minutes	±2 minutes[4]	±5 minutes		
01:00		±10 minutes	±10 minutes[4]	±10 minutes		
01:30		±10 minutes	±10 minutes[4]	±10 minutes		
02:00		±10 minutes	±10 minutes[4]	±10 minutes		
04:00		±10 minutes	±10 minutes[4]	±10 minutes		
06:00		±10 minutes	±10 minutes[4]	±10 minutes		

IP=investigational product, MCQ=multiple choice question, PK=pharmacokinetic, VAS=visual analog scale.

1. IP administration.
2. IP collection.
3. The pre-use PK sample may be collected at any time between -10 minutes and -1 minute before the start of IP use, but after the pulse rate assessment at -15 minutes (± 5 minutes).
4. Pulse rate (pulse oximetry) measurement should be done within -1 minute prior to each PK blood sampling, if possible.
5. Only "craving" at -10 minutes.

11.2 Demographics and other baseline characteristics

11.2.1 Informed consent

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 14.3.

11.2.2 Demographic information

The following demographic data will be recorded at screening (Visit 1): sex, age, ethnicity, and race.

11.2.3 Medical/surgical history

Medical/surgical history will be obtained by subject interview at screening (Visit 1) to verify that the eligibility criteria are met.

11.2.4 History of and current nicotine use

A history of prior nicotine use will be obtained by subject interview at screening (Visit 1) to confirm eligibility. The following information will be collected:

- nicotine product brands,
- average daily consumption in the last 30 days,
- duration of use (years, months),
- history of smoking (number of cigarettes smoked per day in the last 30 days), and
- history of vaping (number of days vaping in the last 30 days).

11.2.5 Eligibility criteria

Eligibility criteria will be checked during screening (Visit 1) and confirmed before randomization and first IP use at Visit 2.

Eligibility criteria are detailed in Sections 9.4 (inclusion) and 9.5 (exclusion).

11.2.6 Height, weight, and body mass index

During screening (Visit 1), weight and height will be measured without shoes. BMI will be calculated, with one decimal, from the recorded height and weight.

11.2.7 Physical examination

A physical examination will be performed during screening (Visit 1) and will include assessment of the head, eyes, ears, nose, throat, skin, thyroid, nervous system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities.

11.2.8 Vital signs

Systolic and diastolic blood pressure and pulse will be measured during screening (Visit 1) in a supine position after 10 minutes of rest.

Pulse rate assessments will be considered ”normal” if within the following ranges:

- At screening (Visit 1): 40 to 90 beats per minute (bpm)
- During IP use visits (Visits 2 to 4): 40 to 100 bpm (refer to Section 11.4.3.1).

11.2.9 Electrocardiogram measurement

Single 12-lead ECGs will be recorded during screening (Visit 1) in a supine position after 10 minutes of rest using an ECG machine. The resting heart rate and PQ/PR, QRS, QT, and QTcF intervals will be recorded.

ECGs will be reviewed and interpreted on-site by the Investigator.

11.2.10 HIV and hepatitis B/C

Subjects will be tested for HIV-1 and HIV-2 antibodies, HIV-1 p24 antigen, hepatitis B virus surface antigen, and hepatitis C virus antibodies prior to inclusion into the study. Any positive result will exclude the subject from participating in the study.

11.2.11 Pregnancy test

All female subjects of childbearing potential will undergo a urine dipstick pregnancy test (urinary human chorionic gonadotropin [U-hCG]) at the screening visit and at Visit 2 (Table 8.2-1). Additional pregnancy tests may be performed at Visits 3 and 4 at the discretion of the Investigator.

11.2.12 Drug screen

Urine will be screened for drugs of abuse/recreational drugs at the screening visit and at Visit 2 (Table 8.2-1), using a Drug Screen Multi-15 Dip Test. Additional drug screening may be performed at Visits 3 and 4 at the discretion of the Investigator.

11.2.13 Alcohol test

Urine alcohol tests will be performed at the screening visit and at Visit 2 (Table 8.2-1). Additional alcohol testing may be performed at Visits 3 and 4 at the discretion of the Investigator.

11.2.14 Baseline symptoms

A baseline symptom is defined as an event that occurs between the subject's signing of the ICF and the first use of IP (*i.e.*, an event that occurs during the screening period). Such events are not AEs but will be recorded as baseline symptoms in the AE log in the eCRF.

11.2.15 Prior and concomitant medications

Prior medications taken within two weeks prior to screening (Visit 1) will be obtained by subject interview to verify that the eligibility criteria are met.

Medications are classified as prior if the stop date was before or on the day of the first IP use (pre dose), and as concomitant if ongoing on the day of the first IP use, stopped after the first IP use, or started after the first IP use. To distinguish between prior and concomitant medications on the first IP use visit (Visit 2), the start time of any newly introduced medication or the stop time of any previously ongoing medication must be recorded in the eCRF.

Any use of prior/concomitant medication from the screening visit until the last visit (Visit 4) must be documented appropriately in the subject's eCRF. Relevant information (*i.e.*, name of medication, dose, dose form, unit, route, frequency, start and stop dates, and reason for use) must be recorded. All changes in medication must be noted in the eCRF.

11.3 Assessments related to the primary endpoint

11.3.1 Blood sampling for nicotine plasma concentration and pharmacokinetic analysis

Venous blood samples (approximately 3 mL) for determining plasma nicotine concentrations and PK characterization after IP use will be collected via venipuncture or an indwelling venous catheter at the pre-specified visits and time points detailed in Table 8.2-2. Blood PK sampling must not deviate from the planned time points beyond the allowed limits outlined in Table 11.1-1.

Pre-dose PK sampling should be conducted -10 minutes to -1 minute before the first IP use.

The date and time of collection of each sample will be recorded in the eCRF.

The blood samples will be collected in pre-labeled tubes. All the collected blood samples will be centrifuged for 10 minutes at 20°C (± 4°C) to separate the plasma within 60 minutes from when the sample was drawn. The separated plasma from each blood sample will be divided into two aliquots in pre-labeled cryotubes and frozen at -70°C within 1 hour after the centrifugation. Further details will be described in a separate laboratory manual.

Plasma samples for determination of plasma concentrations of nicotine will be analyzed by Lablytica Life Science AB, Uppsala, Sweden, by means of a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The details of the analytical method used will be described in a separate bioanalytical report.

11.4 Assessments related to secondary endpoints

11.4.1 Determination of nicotine extracted from pouches

Used pouches will be collected after 30 minutes (± 1 minute) of use for the determination of residual nicotine in the IPs.

All the collected pouches will be frozen within 60 minutes at -20°C. Pouches for nicotine extraction assessment will be analyzed by Swedish Match North Europe AB (refer to Section 5).

Each pouch will be weighed prior to use, along with unused reference pouches from the same batch. Weighing will be performed by the Sponsor before shipment to the study sites, and the unused reference pouches will be retained by the Sponsor. Study personnel should not weigh pouches after use.

11.4.2 Pharmacokinetic sampling and analysis related to secondary endpoints

PK sampling related to the secondary endpoints is part of the procedure described in Section 11.3.1 above.

11.4.3 Pharmacodynamic effects

The PD effects of the IPs will be assessed by measuring pulse rate (via pulse oximetry) and subjective parameters (through VAS and MCQ) at pre-defined time points as described below and in Table 8.2-2.

11.4.3.1 Pulse rate evaluation

Pulse rate will be monitored using a pulse oximeter and will be spot-assessed at -15 minutes pre use, as well as at the minute prior to each PK sample taken at 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 60 minutes, 1 hour:30 minutes, 2 hours, 4 hours, and 6 hours post use (see Table 8.2-2).

Any post-IP measurements of pulse rate outside of normal ranges will be judged as clinically significant or not clinically significant. The assessment will be recorded in the eCRF. Abnormal post-IP use findings assessed by the Investigator as clinically significant will be reported as AEs. Refer to Section 11.2.8.

Allowed deviations from actual time points are outlined in Table 11.1-1.

11.4.3.2 Subjective outcomes evaluation

Subjective parameters ("craving", "satisfaction", "product liking", and "intent to use again") will be rated through a 100 mm VAS, anchored with "not at all" to "extremely", or "very likely" for the "intent to use again" parameter.

The "craving" parameter will be assessed with the question "Right now, how strong is your urge to snus?" at the pre-defined time points: -10 minutes prior to start of IP use, and 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 60 minutes, 1 hours:30 minutes, 2 hours, 4 hours, and 6 hours post use.

The "satisfaction" parameter will be assessed with the question "Right now, is the product satisfying?" at the pre-defined time points: 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 60 minutes, 1 hour:30 minutes, 2 hours, 4 hours, and 6 hours post use.

In addition, "product liking" and "intent to use again" parameters will be assessed at 30 minutes post use with the questions "How much did you like the product?" and "How likely are you to use this product again in the future?", respectively.

Time points for each of the VAS questions are outlined in Table 8.2-2, and allowed deviations from actual time are outlined in Table 11.1-1.

11.4.4 Adverse event reporting

The Principal Investigator at each study site is responsible for ensuring that all medical staff involved in the study at the respective site are familiar with the content of this section and the content of the CTC standard operating procedures (SOPs) regarding emergencies.

AEs will be handled in accordance with applicable regulations and guidelines [10].

For the purpose of this study, AEs will be assessed in relation to the IPs starting from the first IP use.

11.4.4.1 Definition of adverse event

An AE is defined as any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this IP use.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

11.4.4.2 Definition of serious adverse event

An SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in various situations. These situations may include "important medical events" that, while not immediately life-threatening or resulting in death or hospitalization could jeopardize the subject's wellbeing or require intervention to prevent any of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

11.4.4.3 Time period and frequency for collecting adverse events

All AEs (including SAEs) will be collected from the start of first IP use until the last visit (Visits 2 to 4).

Any AE with a start date on the day of each IP use must be recorded with the start time.

On the last IP use visit (Visit 4), information on new AEs or SAEs, if any, and stop dates for ongoing events must be recorded as applicable.

Investigators will not be obliged to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and they consider the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

11.4.4.4 Collection of adverse events

AEs identified using any of the following methods will be recorded:

- AEs spontaneously reported by the subject.
- AEs observed by the Investigator or medical personnel.
- AEs elicited through non-leading questions from the Investigator or medical personnel.

11.4.4.5 Recording of adverse events

AEs must be recorded in the AE log of the eCRF. The Investigator must provide information on the AE, preferably as a diagnosis or at least as signs and symptoms; start and end dates, start and end time, intensity, causal relationship to IPs, action taken, and outcome. If the AE is serious, this must be indicated in the eCRF.

AEs, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

11.4.4.6 Assessment of seriousness

The Investigator must assess and document the seriousness (serious or non-serious) of each AE using the definitions in Section 11.4.4.2. If the event is assessed as serious it must be reported as an SAE by the Investigator to the Sponsor according to Section 11.4.4.11.

For the seriousness criterion of inpatient hospitalization or prolongation of existing hospitalization to be fulfilled, inpatient hospitalization is defined as the admission of the subject to the hospital for inpatient care, either to an inpatient ward or to an emergency room for observation and/or treatment, that would not have been appropriate in a physician's office or outpatient setting.

Planned hospitalizations or surgical interventions for a condition that existed before the subject signed the ICF, and that did not change in intensity, are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative approach will be taken, and the AE will be reported as an SAE.

11.4.4.7 Assessment of intensity

The grading of the intensity of AEs will follow the common terminology criteria for adverse events (CTCAE) version 6.0 [11]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the intensity of an AE using the following definitions, and record it in the AE log of the eCRF:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4 Life-threatening consequences: urgent intervention indicated.

Grade 5 Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc.*

**Self-care ADL refers to bathing, dressing, undressing, feeding self, using the toilet, taking medications, and not being bedridden.

11.4.4.8 Assessment of causal relationship

The Investigator must assess the causal relationship between an AE and the use of the IPs using the definitions below. Each assessment should be recorded in the AE log of the eCRF.

Probable	The event has a strong temporal relationship to the IP or recurs upon re-challenge and another etiology is unlikely or significantly less likely.
Possible	The event has a suggestive temporal relationship to the IP, and an alternative etiology is equally or less likely.
Unlikely	The event has no temporal relationship to the IP or is attributable to an underlying or concurrent illness or the effect of another drug (*i.e.*, there is no causal relationship between the IP and the event).

An AE is considered causally related to the use of the IP when the causality assessment is probable or possible.

11.4.4.9 Outcome of adverse event

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE log of the eCRF.

Recovered/resolved	The subject has recovered completely, and no symptoms remain.
Recovering/resolving	The subject's condition is improving, but symptoms remain.
Recovered/resolved with sequelae	The subject has recovered, but some symptoms remain (*e.g.*, the subject had a stroke and is functioning normally but has some motor impairment).
Not recovered/not resolved	The subject's condition has not improved, and the symptoms are unchanged (*e.g.*, atrial fibrillation has become chronic).
Fatal	
Unknown	

11.4.4.10 Action taken with investigational product

The Investigator must document the action taken with the IP using one of the options "Dose not changed", "Drug interrupted", "Drug withdrawn", "Not applicable", or "Unknown", and record it on the AE log of the eCRF.

11.4.4.11 Reporting of serious adverse events

The Investigator must report SAEs within 24 hours of awareness to the Sponsor or its designee; this includes both initial information and any subsequent relevant/significant follow-up information to a previously reported SAE. The primary mechanism for reporting an SAE will be via the eCRF. When the Investigator classifies the event as "serious" in the eCRF, and signs off the event, an automatic e-mail alert is sent to the Sponsor or its designee, and any other pre-defined recipients.

The backup procedure for reporting an SAE, in case the eCRF is unavailable, will be via the paper SAE form provided in the investigator site file (ISF). The Investigator must complete the SAE form and send it to the Sponsor or its designee. The study site must notify the site Monitor by phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE must be reported electronically as well. The completed, signed, and dated paper SAE form should be scanned and delivered within 24 hours via encrypted e-mail or secure file transfer to:

[redacted]

A copy of the SAE paper form must also be delivered via encrypted e-mail or secure file transfer to: [redacted].

All available information regarding the SAE must be entered in the AE log for the specific subject, *i.e.*, AE term, intensity, causality, outcome, seriousness criteria, action taken with IP, and a narrative including the Investigator's rationale for the causality assessment.

The SAE report will be reviewed by the Sponsor or its designee to ensure that the report is valid. The Sponsor or its designee will acknowledge receipt of the SAE report to the reporting Investigator. For SAEs where important or relevant information is missing, follow-up queries to the site are raised promptly to keep the regulatory reporting timelines.

The Sponsor will perform an independent assessment of causality, including a rationale for the assessment. The causality assessment given by the Investigator should not be downgraded by the Sponsor. If the Sponsor disagrees with the Investigator's causality assessment, the opinion of both the Investigator and the Sponsor should be provided in the report.

If any additional information or documentation (*e.g.*, autopsy report) on the SAE is required for the Sponsor's assessment of the SAE, the Sponsor or its designee will request this information from the Investigator, and the Investigator is required to promptly respond to the request.

Any subsequent relevant/significant follow-up information to a previously reported SAE must be entered in the AE log for the specific subject. If the Investigator makes any changes to the assessment of the case *e.g.*, changes in seriousness, causality, or intensity, a justification for the change should be provided in the case narrative. If the SAE report in the eCRF is updated, a new automatic e-mail alert is sent to the Sponsor or its designee.

Detailed information on the SAE handling will be described in a study-specific safety management plan.

11.4.4.12 Treatment and follow up of adverse events

Subjects with AEs that occur during the study must be treated according to daily clinical practice at the discretion of the Investigator.

AEs must be followed-up until resolution or until the last visit (Visit 4), whichever occurs first. At the last visit, information on any new AEs and stop dates for previously reported AEs must be recorded, if known. AEs assessed as stable by the Investigator at the last IP use visit do not need to be followed-up until resolution.

It is the responsibility of the Investigator to follow up on all SAEs until the subject has recovered, stabilized, or recovered with sequelae, and to report all relevant new information to the Sponsor using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultations.

11.4.4.13 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy, the study IP use must be stopped immediately, and the subject should be withdrawn from the study.

Pregnancy itself will not be considered an AE unless there is a suspicion that the IP may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies must be followed up by the Investigator and the Sponsor and documented even after the subject has been discontinued from the study.

All pregnancies must be reported immediately by the Investigator to the Sponsor or designee using the pregnancy report form provided in the ISF. Once known, information on the pregnancy outcome must also be reported to the Sponsor or designee using the same form.

Any adverse pregnancy outcomes will be considered SAEs and must be handled and reported accordingly, as described in Section 11.4.4.11.

11.4.4.14 Treatment of overdose

An overdose is defined as a dose exceeding the amount specified for a subject in this CSP.

Overdosing is unlikely in this study since all IPs will be administered as single doses by site personnel under medical surveillance. In the event of an accidental overdose, standard supportive measures will be implemented as required.

Overdoses must be documented in the eCRF. An overdose associated with an AE should be recorded as the AE diagnosis/symptoms in the AE log of the eCRF. An overdose without associated symptoms should only be reported in the subject's medical records and documented in the PD log.

11.5 Assessments related to exploratory endpoints

11.5.1 Exploratory subjective parameters

[redacted]

11.5.2 Nicotine extraction-normalized pharmacokinetic parameters

Nicotine extraction and PK sampling related to exploratory endpoint no. 2 are included in the procedures described above in Section 11.4.1 and Section 11.3.1, respectively.

11.6 Appropriateness of measurements

All methods used are commonly applied in standard medical care and in phase I clinical studies. Non-compartmental analysis of PK parameters is standard for phase I clinical studies.

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

The sample collection procedure for PK analysis is described in Section 11.3.1.

12.2 Volume of blood

The anticipated volume of blood samples collected from screening (Visit 1) through Visit 4 for each subject will be approximately 111.5 mL (Table 12.2-1). For reference, a regular blood donation consists of between 350 mL to 450 mL (±10%) and is typically collected on a single occasion from individuals weighing at least 45-50 kg [12].

Additional blood samples for safety evaluations may be collected at the discretion of the Investigator.

Table 12.2-1 Estimated blood volumes

Assessment	Estimated number of sampling occasions	Estimated volume per occasion (mL)	Total (mL)
PK blood sampling	36	3 mL	108 mL
HIV, Hepatitis B/C	1	3.5 mL	3.5 mL
		Total:	111.5mL

12.3 Handling, storage, and destruction of laboratory samples

All biological samples will be registered in a biobank at CTC (Swedish Health and Social Care Inspectorate biobank registry number 893).

Any remaining laboratory samples will be disposed of after analysis.

The samples for analyses of plasma PK parameters will be stored at ≤ -70°C until analyzed. The samples will be disposed of after the CSR has been finalized.

12.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

CTC keeps full traceability of collected biological samples from the study subjects while in storage at the study site until shipment and keeps documentation of receipt of arrival. The sample receiver (the analytical laboratory) will maintain full traceability of the samples during their storage and analysis, until they are either used up or disposed of.

The Sponsor will keep oversight of the entire lifecycle of the samples through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

12.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of biological samples donated, the samples will be disposed of/destroyed, if not already analyzed and documented.

The Principal Investigator at each site will ensure that:

- Subject withdrawal of consent is notified immediately to the Sponsor.
- Biological samples from the subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action is documented.

The Sponsor must ensure that the laboratory/laboratories holding the samples is/are immediately informed about the withdrawn consent, and that samples are either disposed of, destroyed, or returned to the study site, with the action documented.

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Statement of compliance

The clinical study will be conducted in accordance with this CSP, CTC's SOPs, and the applicable sections of the following regulations and guidelines:

- European Union (EU) clinical trials regulation – Regulation (EU) no.536/2014 [10],
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R3) guideline [13],
- Declaration of Helsinki and its amendments [14].

The clinical study will not be initiated until the required approval and favorable opinion from the applicable IEC have been obtained. Any additional requirements imposed by the IEC will be followed.

13.2 Quality management: critical processes, systems, and data identification

During CSP development, the Sponsor will identify those processes, systems (facilities, computerized systems), and data that are critical to ensure human subject protection and the reliability of study results according to applicable SOPs and the ICH E6(R3) guideline [13].

Identified critical-to-quality factors, associated risks, quality tolerance limits (QTLs), and risk mitigation actions will be described and categorized in the study risk log.

Risk-based quality management in line with the ICH good clinical practice (GCP) guideline E6 (R3) [13], is established for this study. The procedures to identify, assess, control, communicate, and review risks associated with the conduct of this clinical study are defined in CTC's SOPs. The risk log will be reviewed regularly during the study, and mitigation actions updated, as required.

Prior to study initiation, the Sponsor will define QTLs for relevant risks related to the study conduct and performance. The definition of QTLs, along with pre-defined thresholds, sub-thresholds, and actions, will be included in the risk log. QTLs will be monitored continuously during the study and reviewed at project management meetings.

13.3 Quality assurance and quality control

The Sponsor has delegated the responsibilities outlined below to CTC while maintaining overall study oversight:

- Implement and maintain quality assurance and quality control systems with written SOPs addressing the management of identified risks, CSP compliance, GCP compliance, and applicable regulatory requirements.
- Secure agreements with involved subcontractors and performing regular subcontractor oversight to ensure CSP compliance, GCP compliance, and compliance with applicable regulatory requirements.
- Implement a risk-based validated EDC system and maintain SOPs for the entire life cycle of the system.
- Apply quality control at each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.4 Deviations from the clinical study protocol

A protocol deviation occurs when the Investigator or site personnel do not conduct the clinical study in accordance with GCP, the CSP, or clinical study agreements.

The Investigator is not permitted to deviate from these documents, except under emergency circumstances to eliminate an immediate hazard to study subjects. In such cases, the Investigator must inform the Sponsor promptly.

All protocol deviations must be documented. In addition to those identified by the Investigator, deviations relevant to their study subjects and study conduct may be communicated by the Sponsor. In either case, the Investigator should review the deviations and, for those deemed important, provide an explanation and implement appropriate measures to prevent recurrence, where applicable.

Reporting time frames and escalation routes for protocol deviations will be specified in the risk-based monitoring (RBM) plan.

All protocol deviations will be classified as important or non-important prior to database lock. Important protocol deviations are those that may significantly impact the completeness, accuracy, or reliability of the study data, or that may significantly affect a subject's rights, safety, or wellbeing.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The clinical study will be performed in accordance with ethical principles and regulations outlined in Section 13.1.

14.2 Ethics and regulatory review

The Coordinating Investigator is responsible for submitting the CSP, the subject information, and the ICF, any other written information to be provided to the subjects, and any advertisements used for subject recruitment, to the applicable IEC for approval.

Written approval from the IEC must be obtained before the first subject can be recruited.

The Sponsor will provide the IEC and Coordinating Investigator with safety updates and reports in accordance with local requirements.

14.3 Subject information and consent

It is the responsibility of the Investigator or an authorized associate to give each potential study subject adequate verbal and written information before any study-specific assessments are performed.

The information will include the nature, objectives, implications, risks, and inconveniencies of the study, as well as the conditions under which the study will be conducted and the expected duration of participation. It will be emphasized that participation in the study is voluntary and that the subjects may withdraw at any time and for any reason, without any detriment and without having to provide justification. All subjects will be given the opportunity to ask questions and sufficient time to consider participation before signing and dating the ICF.

Before performing any study-related procedures, the ICF must be signed and personally dated by both the subject and the Investigator. A copy of the subject information, including the signed and dated ICF, will be provided to the subject.

Documentation of the discussion and the date of informed consent must be recorded in the source records and in the eCRF. The subject information sheet and the signed and dated ICF should be filed by the Investigator for possible future audits and/or inspections.

The final approved version of the subject information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

14.4 Subject privacy and data protection

The clinical personnel affirm and uphold the principle of the subject's right to privacy during and after the study.

The ICF includes information that data will be recorded, collected, and processed, and information related to potential transfer to European Economic Area (EEA) or non-EEA countries. In accordance with the general data protection regulation (GDPR [EU] 2016/679) [15], pseudonymized data will not identify any individuals participating in the study. If any part of the data, including biological samples, is handled by an organization, whether inside or outside the EU, appropriate agreements, such as data transfer agreements, will be established. These agreements will define the parties' roles and responsibilities and outline how individuals may exercise their rights with respect to the data.

Prior to any data transfer agreement, verification of the receiving organization's quality and process systems will be conducted to ensure that data processing complies with the GDPR and other applicable legislation.

The potential subject should be informed that by signing and dating the ICF they approve that the authorized representatives from the Sponsor and CTC, as well as the concerned IEC, have direct access to their medical records for verification of clinical study procedures. For further details on the subject information and ICF process, refer to Section 14.3.

The subject has the right to request access to their personal data and the right to request rectification of any data that is not correct and/or complete in accordance with the GDPR [15], and the request will be raised to the Principal Investigator at the applicable study site.

The Investigator must file a subject identification list that includes sufficient information to link records, *i.e.*, the eCRF and clinical records. This list must be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.

Personal data that are collected in the study, such as health information and ethnicity, are considered sensitive personal data. This data will be pseudonymized, *i.e.*, personally identifiable information will be removed and replaced by a unique subject ID and will be processed by the Sponsor and other involved parties during the study. After the study ends, only pseudonymized data, *i.e.*, aggregated data sets, can be used.

For this study, the Sponsor is the data controller of all data processed during the study (*e.g.*, TMF and study reports), and CTC is the data processor. Any subcontractors used in the study are also data processors.

For data that are processed at the study sites (*e.g.*, medical records and ISF), CTC is the data controller.

14.5 Data security breach

To prevent or minimize data security breaches, organizational, physical, and technological safeguards have been implemented across all computer systems used to process data and personal data in this study, following a risk-based approach.

In the event of a data security breach, the data controller (defined as the Sponsor for study data and the study site for medical data) must:

- document all personal data breaches, including the facts surrounding the breach, its effects, and the remedial action taken;
- notify the supervisory authority of the breach, unless it is unlikely to result in a risk to the rights and freedoms of natural persons; and
- inform the affected subjects if the breach is likely to result in a high risk to their rights and freedoms.

14.6 Changes to the approved clinical study protocol

Any proposed change to the approved final CSP, including its appendices, must be documented in a written and numbered clinical protocol modification form. All substantial modifications to the CSP must be approved by the concerned IEC according to applicable regulations before implementation.

14.7 Audits and inspections

Authorized representatives of the Sponsor and/or the concerned IEC may perform audits or regulatory inspections at the study site, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documentation to determine whether these activities were conducted and data recorded, analyzed, and reported in accordance with the CSP, ICH GCP guidelines, and applicable regulatory requirements. The Principal Investigator at the applicable study site must immediately notify the Sponsor if contacted by the IEC regarding an inspection.

14.8 Insurance

Subjects will be covered under the Sponsor's liability insurance policy through Chubb European Group SE, United Kingdom. The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating subjects are also protected in accordance with national regulations, as applicable.

CTC has company insurance covering medical procedures and services performed by CTC. The certificate of insurance can be provided upon request.

15 STUDY MANAGEMENT

15.1 Training of study site personnel

Before the inclusion of the first study subject, a Sponsor representative or delegate will perform a site initiation visit at the study sites. The requirements of the CSP and related documents will be reviewed and discussed, and the investigational staff will be trained in any study-specific procedures and system(s) utilized.

It is the responsibility of the Principal Investigator at each study site to ensure that all personnel involved in the study at the respective site are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Principal Investigator at each study site will keep a list of all personnel involved in the study at the respective site, together with their function and study-related duties delegated. A *Curriculum Vitae* will be available for all staff delegated study-specific duties.

15.2 Clinical monitoring

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all participating sites, source data/records, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities. The extent and nature of the monitoring shall be determined by the Sponsor based on a risk assessment that considers all relevant characteristics of the clinical study.

As defined in the RBM plan, approved by the Sponsor and provided separately, the responsible Monitor will periodically visit the study sites at times agreed upon by the Principal Investigator at the applicable site and the Monitor. At each monitoring visit, the role of the Monitor is (but not limited to) the following:

- to provide information and support to the investigational team,
- to confirm that facilities and resources remain acceptable,
- to confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals, and regulatory requirements,
- to verify that data are being accurately and timely recorded in the eCRFs and that IP accountability checks are being performed,
- to verify that data in the eCRF are consistent with the clinical records (*i.e.*, SDV) in accordance with the RBM plan,
- to verify that the correct informed consent procedure has been adhered to for participating subjects,
- to ensure that withdrawal of informed consent to the use of the subject's biological samples will be reported and biological samples are identified and disposed of/destroyed accordingly, and that this action is documented and reported to the subject,
- to verify that AEs are recorded and reported in a timely manner and according to the CSP,
- to raise and escalate any serious quality issues, serious GCP breaches, and any data privacy breaches to the Sponsor.

Centralized monitoring will also be performed continuously by project team members at CTC in accordance with the RBM plan. When the study has been completed, all queries have been resolved, and the database has been locked, and the Monitor will perform a close-out visit.

15.3 Source data records

A separate origin of source data list will be generated for each study site before the start of enrollment, specifying the location of the source of derived information appearing in the eCRF. This document must be signed by the Principal Investigator at each study site and the Monitor to confirm agreement before the start of recruitment.

Source records are all documents used by the Investigators or hospital that relate to the subject's medical history, and that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, memoranda, material dispensing records, subject files, *etc.* The eCRF may constitute source data if clearly defined in the origin of the source data list.

The Principal Investigator at each study site must ensure access to source records for the Monitor, and, if required, the applicable IEC.

15.4 Study agreements

This study is fully financed by the Sponsor, Swedish Match North Europe AB. The management and conduct of the clinical study have been outsourced to the contract research organization (CRO), CTC. The Coordinating/Principal Investigators are employees of CTC.

The agreements between the Sponsor and CTC must be in place before any study-related procedures take place or subjects are enrolled.

The Sponsor and CRO responsibility and duty split is regulated in a separate clinical study agreement.

The Principal Investigator at each study site must comply with all the terms, conditions, and obligations of the clinical study agreement for this clinical study.

15.5 Study timetable and end of study

The study is expected to start in Q1 2026 and to be completed by Q2 2026.

A subject is considered to have completed the study if they have completed all visits in the study, including the last visit (Visit 4).

The start of the study is defined as the date of the first subject's first visit (Visit 1). The end of the study is defined as the date of the final CSR.

15.6 Temporary halt of early termination of the study

The Principal Investigator at each study site or the Sponsor may temporarily halt or terminate the study prematurely for any reasonable cause. A temporary halt or early termination must be reported to the applicable IEC without undue delay. The reason for the halt or termination and any specific follow-up measures should be clearly stated.

Conditions that may warrant study termination include, but are not limited to, safety concerns or a decision by the Sponsor to suspend or discontinue development of the IP.

If the study is prematurely terminated or suspended for any reason, the Principal Investigator at each study site must promptly inform enrolled subjects at the respective site and ensure appropriate follow up for those subjects.

15.7 Reporting and publication

15.7.1 Clinical study report

After completion of the study, an ICH E3 [16] compliant CSR describing the conduct of the study, any statistical analyses performed, and the results obtained will be prepared by the Sponsor or their designee. The CSR will be reviewed and approved by, at a minimum, the Coordinating Investigator, the Statistician, and the Sponsor.

All results obtained from any exploratory analyses may be reported separately.

15.7.2 Confidentiality and ownership of study data

Any confidential information relating to the IPs or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study are responsible for protecting the confidentiality of this proprietary information.

15.7.3 Publication

The results from this study may be submitted for publication at the discretion of the Sponsor.

15.8 Archiving

The Principal Investigator at each study site is responsible for maintaining essential documents (as defined in Section 8 of ICH E6(R3) [13]) for 25 years after finalization of the CSR. This includes original source records related to the study, the subject identification list (providing the sole link between named subject source records and pseudonymous eCRF data), the original signed ICFs, and detailed records of IP disposition.

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

The Sponsor will archive the TMF in accordance with Section 8 of the ICH E6(R3) guideline [13] and applicable regulatory requirements.

Data from the eCRFs will be sent to the Sponsor, and a copy will be sent to the study sites and filed in the ISF for archiving for 25 years after finalization of the CSR.

The completed original eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of appropriate health/regulatory authorities, without written permission from the Sponsor.

16 DATA MANAGEMENT

The data management routines include procedures for handling the eCRF, database setup and management, data entry and verification, data validation, quality control of the database, and documentation of the performed activities, including information on discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CSP.

Data validation/data cleaning procedures are designed to assure the validity and accuracy of clinical data. These procedures consist of computerized online edit checks, identifying *e.g.*, data values that are outside the allowed range, and SAS-programmed batch checks on data exports. All study-specific and standard data validation programming will be tested prior to being used on the final data.

Detailed information on data management will be described in a study-specific data management plan.

16.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF (Viedoc™) provided by Viedoc Technologies AB. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source records or at the bedside (if the eCRF data constitutes source data). Source data are to be defined at the sites before the inclusion of the first subject (Section 15.3).

Authorized site personnel designated by the Principal Investigator at each study site will complete data collection. Appropriate training and security measures will be completed with the respective Principal Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any study subject.

16.2 The entering of data into the eCRF

All entries, corrections, and alterations are to be made by the Principal Investigators or designees. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF. All data should be entered in English. The eCRFs should be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the Investigator or assigned clinical staff will record such information in the eCRF.

The Investigator will be required to electronically sign off on the clinical data. This will be performed by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at the time of electronic signature.

16.3 The query process

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source records to ensure that there are no discrepancies for critical data as described in the RBM plan. All entries, corrections, and alterations are to be made by the Investigator or designee.

If corrections are needed, queries will be raised within the eCRF, either as a result of built-in edit checks or manually raised by the Monitor. An appropriate member of the site staff will answer the queries in the eCRF either by correcting the data or by entering a response to the query.

16.4 Audit trail

All entries in the eCRF will be fully recorded in a protected audit trail. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for the change, the name of the person who made the change, together with the time and date will be logged.

16.5 External data

External data consists of data that are not recorded in the eCRF. Data may be received in electronic format. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed upon with the external data provider through a data transfer agreement.

16.6 Medical coding

Medical coding will be performed by trained personnel at CTC. AEs and medical/surgical history verbatim terms are coded using the Medical Dictionary of Regulatory Activities (MedDRA, latest version available at eCRF setup).

Prior and concomitant medications will be coded according to the World Health Organization (WHO) anatomic therapeutic chemical (ATC) classification system (latest version available at eCRF setup). All coding will be approved by the Sponsor prior to database lock.

16.7 Database lock

When all data has been entered and discrepancies solved, clean file will be declared, the database will be locked, and the data will be analyzed.

17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate statistical analysis plan (SAP), which will be signed and approved prior to database lock.

17.1 General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value, and interquartile range (IQR), Q3-Q1.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by IP, and by assessment time. Individual subject data will be listed by subject number, IP, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC, US). The PK parameters will be calculated using non-compartmental analysis with the Phoenix WinNonlin® software version 8.6 or later (Certara Inc., Princeton NJ, US).

Baseline will be defined as the last non-missing data collection point prior to each IP use.

No adjustment for multiple comparisons will be performed. All significant findings will be reviewed for clinical relevance.

All collected data will be listed by subject.

17.2 Missing, unused and spurious data

Generally, no imputation of data will be performed. In case of missing start and stop times of AEs that cannot be investigated further, missing data will be imputed according to a worst-case scenario, *i.e.*, start time will be imputed as the closest time point post IP administration and end time as 23:59, resulting in the longest possible treatment-emergent duration of the AE.

When calculating descriptive statistics for plasma concentrations, the concentrations below the lower limit of quantification (LLOQ) will be replaced by LLOQ/2 if more than 50% of the values for a given time point are above LLOQ. Otherwise, no descriptive statistics will be calculated for plasma concentrations at that time point. The imputation of PK plasma concentrations below LLOQ with the purpose of calculating PK parameters will be described in detail in the SAP.

Spurious data will be continuously evaluated through data validation (see Section 16). If associated with protocol deviations, such data will be assessed on a case-by-case basis prior to the declaration of clean file and database lock, at the latest.

Deviations from the original SAP will be described in the CSR.

The handling of missing, unused, and spurious data may be further detailed in the SAP.

17.3 Determination of sample size

The sample size was calculated assuming a 2 × 2 crossover design analyzed on a log scale, and is based on the primary endpoint comparison to assess similarity in $AUC_{0\text{-}inf}$ between NP1 (Smooth, 1.5 mg) and NP2 (Wintergreen, 1.5 mg).

The parameters assumed in the power calculation used to determine sample size are detailed in Table 17.3-1 below.

Table 17.3-1 Power calculation

Input	Value	Comment
Power	80%	Nominally set.
Alpha	5%	Two one-sided tests of alpha = 5% are used.
Hypothesized true geometric least square means ratio	1	
Similarity bounds for the geometric LSMeans ratio	0.8 to 1.25	
Coefficient of variation (CV)	0.325	As observed in previous studies.
Assumed drop-out rate	~14%	Forty-two (42) subjects will be randomized to achieve 36 evaluable subjects for the primary endpoint.
Total sample size	42	

LSMeans=least squares means.

Forty-two (42) subjects will be randomized to achieve at least 36 evaluable subjects, defined as those who receive both NP1 and NP2 products, and have reliable $AUC_{0\text{-}inf}$ values for each product.

Efforts will be made to randomize at least 40% of subjects from the least represented sex, corresponding to about 14 subjects. However, a minimum of 20% (about seven subjects) will be considered acceptable.

17.4 Analysis data sets

17.4.1 Full analysis set

The Full analysis set (FAS) will consist of all subjects who have been randomized. This population will be used for the safety analysis set.

17.4.2 PK analysis set

The PK analysis set (PKAS) will consist of all subjects who used at least one IP and provided at least one evaluable PK profile, and no major deviation or AEs judged to compromise the PK analysis. Individual PK values and/or full profiles for explicit IPs may be excluded from the analysis as specified in the SAP.

17.5 Pharmacokinetic analysis – General

The PK analysis will be based on the PKAS and performed by CTC. Non-compartmental PK parameters will be determined in relation to the primary endpoint (see Section 17.7.1) as well as secondary endpoints (see Section 17.8.2). Where feasible, both baseline-adjusted and non-adjusted PK parameters will be calculated.

For $AUC_{0\text{-}inf}$, the area under the plasma concentration *vs*. time curve will be calculated to the time point of the last quantifiable plasma concentration of nicotine and then extrapolated to infinity using the concentration in the last quantifiable sample and the estimated terminal elimination rate constant ($Lambda_z$).

PK data will be presented for each IP using summary statistics. This data will be presented in terms of N, arithmetic mean, median, SD, as well as minimum and maximum value. For applicable PK parameters, the geometric mean and coefficient of variation (CV%) will be presented. Categorical data will be presented as counts and percentages, as applicable.

17.6 Description of study population

17.6.1 Demographics and baseline characteristics

Descriptive statistics for demographics, weight, height, BMI, as well as history of prior nicotine use will be presented.

17.6.2 Medical/surgical history and prior/concomitant medication

Medical/surgical history will be presented by system organ class (SOC) and preferred term (PT). Prior/concomitant medications will be presented by ATC levels 4 and 5.

17.6.3 Investigational product use

The number of subjects who used each IP will be presented through listings.

17.6.4 Physical examination

Physical examination parameters will be specified as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant” (as judged by the Investigator at the screening visit) and summarized.

17.6.5 Vital signs

Vital signs (systolic/diastolic blood pressure, and pulse rate) will be summarized.

17.6.6 Electrocardiogram

All ECGs will be categorized as ”normal”, ”abnormal, not clinically significant”, or ”abnormal, clinically significant” (as judged by the Investigator at the screening visit) and summarized.

17.7 Analysis of primary endpoint

17.7.1 Similarity in baseline-adjusted $AUC_{0\text{-}inf}$

The primary objective of this study is to assess whether the unflavored NP1 product (Smooth, 1.5 mg) and the flavored NP2 product (Wintergreen, 1.5 mg) result in similar nicotine exposures, measured as baseline-adjusted $AUC_{0\text{-}inf}$.

The similarity between baseline-adjusted $AUC_{0\text{-}inf}$ for the two IPs will be assessed using a mixed model. In this model, the log-transformed $AUC_{0\text{-}inf}$ will be the dependent variable, the product will be the fixed effect, and the subject within the sequence will be the random effect. The Kenward-Roger improved method [17] will be used to estimate the denominator degrees of freedom. The estimated least square mean difference between products and the associated confidence interval (CI) will be back-transformed to the original scale to present the ratio of geometric least square means, along with the corresponding 90% CI.

Similarity will be concluded if the point estimate for the ratio of $AUC_{0\text{-inf}}$ from the model (NP1/NP2) falls within the similarity acceptance interval of 0.8-1.25 (80.00-125.00%).

17.8 Analysis of secondary endpoints

17.8.1 In vivo extracted amount and fraction of nicotine

The nicotine content of an unused reference pouch and the used study pouch will be used to calculate the *in vivo* extracted amount and fraction of nicotine for each IP. Extracted amounts and fractions of nicotine will be presented using summary statistics. The amount of nicotine in the reference pouches will be presented through descriptive statistics.

Further details will be provided in the SAP.

17.8.2 Pharmacokinetics of nicotine in plasma

The following non-compartmental PK parameters will be assessed in the study, provided sufficient data are available:

- area under the plasma concentration *vs.* time curve (AUC) from time 0 extrapolated to infinity ($AUC_{0\text{-inf}}$),
- AUC from time 0 to the time of the last measurable plasma concentration ($AUC_{0\text{-last}}$),
- AUC from time 0 to 1.5 hours post use ($AUC_{0\text{-1.5h}}$),
- maximum observed plasma concentration (C_{max}),
- time to C_{max} (T_{max}), and
- terminal elimination half-life ($T_{1/2}$).

Where feasible, both baseline-adjusted and non-adjusted PK parameters will be calculated.

C_{max} and T_{max} will be derived from the observed nicotine plasma concentration data. $AUC_{0\text{-1.5h}}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ will be calculated through log-linear trapezoidal interpolation. Calculations will be based on the actual sampling times recorded during the study. Concentrations below LLOQ occurring before C_{max} will be treated as zero. Concentrations below LLOQ occurring after C_{max} will be omitted from the analysis. All baseline-adjusted PK parameters will be corrected for nicotine plasma concentrations at baseline (pre use).

$AUC_{0\text{-inf}}$ will be calculated as described in Section 17.5 above.

In addition, descriptive statistics for secondary PK parameters and concentrations (baseline-adjusted and non-baseline-adjusted) will be presented. PK plasma concentration curves over time will be presented.

Further details will be provided in the SAP.

17.8.3 Similarity in baseline-adjusted C_{max}

The similarity between baseline-adjusted C_{max} for the unflavored NP1 product (Smooth, 1.5 mg) and the flavored NP2 product (Wintergreen, 1.5 mg) will be assessed using the same approach as for the primary endpoint, refer to Section 17.7.1.

17.8.4 Pharmacodynamic effects

Oximeter pulse rates will be summarized in descriptive tables and displayed as mean plots over time for each IP.

The subjective parameters "craving" and "satisfaction", measured by VAS, will be summarized for each IP using descriptive statistics during the IP use phase and until 6 hours after the start of IP use. The absolute change from baseline will be calculated for "craving" for each IP and summarized. The subjective parameters "product liking" and "intent to use again" will be assessed only upon removal of the IPs (after 30 minutes of use) and summarized accordingly.

To determine the maximum PD effect attributable to the IP, the maximum increase from baseline (E_{imax}), time to the first instance of E_{imax} (T_{Eimax}), the E_{max} from time 0 to 60 minutes post use ($E_{max0-60}$), and the time to reach $E_{max0-60}$ ($T_{Emax0-60}$) will be calculated for pulse rates and presented using descriptive statistics.

For the subjective parameter "craving", the largest decrease from baseline (E_{dmax}) and the time to E_{dmax} (T_{Edmax}) will be calculated and summarized using descriptive statistics.

For the subjective parameter "satisfaction", which does not have a baseline, the largest value (E_{vmax}) and time to E_{vmax} (T_{Evmax}) will be calculated and summarized using descriptive statistics.

17.8.5 Adverse events

An overview of all AEs, including SAEs, their intensity, relationship to the IPs, and any deaths, will be presented by IP. The incidence of AEs and SAEs will be summarized by SOC and PT for each IP.

All AE data will be listed by subject number and include the verbatim term entered by the Investigator.

17.9 Analysis of exploratory objectives

17.9.1 Exploratory subjective parameter

[redacted]

17.9.2 Extraction-normalized AUC_{0-inf} and C_{max}

Nicotine extraction-normalized PK parameters AUC_{0-inf} and C_{max} (both baseline-adjusted and non-adjusted, divided by the extracted amount), will be calculated and summarized for each IP using descriptive statistics.

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19 SIGNATURES

19.1 Approval of the clinical study protocol

I, the undersigned, approve this CSP.

Sponsor signatory

[redacted]

Coordinating Investigator

Björn Schultze, MD
Clinical Trial Consultants AB