Clinical Study Protocol	
Investigational products	Tobacco and nicotine pouches
Study code	SM24-03
Protocol version and date	Final v1.0, 04DEC2024

Effects of single doses of tobacco-based snus and 3 mg nicotine pouches on plasma nicotine, pharmacokinetics, and pharmacodynamics

Test products and dose

Nicotine pouch (NP) 1 - Dry, flavor A – 3 mg
NP 2 – Moist, flavor B – 3 mg
NP 3 – Moist, unflavored – 3 mg
T1 – Tobacco-based snus 1 – 4 mg
T2 – Tobacco-based snus 2 – 8 mg

Sponsor signatory

[redacted]

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

[redacted]

Coordinating Investigator

Björn Schultze, MD
Clinical Trial Consultants AB

Clinical study management

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

1 STUDY SYNOPSIS

Study title

Effects of single doses of tobacco-based snus and 3 mg nicotine pouches on plasma nicotine, pharmacokinetics, and pharmacodynamics.

Study code	**Planned study period**
SM24-03	Q1 2025 to Q3 2025

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, 5-way cross-over, single-dose administration study designed to assess nicotine exposure from three nicotine pouch (NP) products compared to two tobacco-based products. The investigational products (IPs) include two flavored NP products (both 3 mg), one unflavored NP product (3 mg), and two tobacco-based snus products (4 mg and 8 mg).

Objectives and endpoints

Primary objective	**Endpoint**
To demonstrate the similarity in C_{max} between each of the three NP products and at least one of the two tobacco-based products.	Similarity in baseline-adjusted C_{max} based on nicotine plasma concentrations after administering single doses of the three NP products and the two tobacco-based products.

No.	**Secondary objectives**	**No.**	**Endpoints**
1.	To demonstrate equivalence in C_{max} and $AUC_{0\text{-}inf}$ between each of the three NP products and at least one of the two tobacco-based products.	1.	Equivalence (90% CI for the ratio between 0.8 and 1.25) in baseline-adjusted C_{max} and $AUC_{0\text{-}inf}$ based on nicotine plasma concentrations after administering single doses of the three NP products and the two tobacco-based products.
2.	To compare the *in vivo* extracted amount (mg/unit) and extracted fraction (%) of nicotine from the three NP products with those from the two tobacco-based products	2.	The difference in *in vivo* extracted amount (mg/unit) and extracted fraction (%) of nicotine between the three NP products and the two tobacco-based products.
3.	To compare the PK profile between the three NP products and the two tobacco-based products.	3.	The difference between the three NP products and the two tobacco-based products in the non-adjusted and baseline-adjusted PK parameters: $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $AUC_{0\text{-}1.5h}$, $AUC_{0\text{-}last}$, and $T_{½}$.
4.	To assess the PD effects, measured as pulse rate and subjective outcome measures, of the three NP products and the two tobacco-based products.	4a.	PD (pulse rate): The difference between the three NP products and the two tobacco-based products for E_{imax}, T_{Eimax}, $E_{max0\text{-}60}$, and $T_{Emax0\text{-}60}$ in pulse rate, measured using a pulse oximeter after IP use.
		4b.	PD parameters: The difference between the three NP products and the two tobacco-based products for E_{dmax} and T_{Edmax} in the subjective parameter "craving" measured using a 100 mm VAS after IP use.

		4c.	PD parameters: The difference between the three NP products and the two tobacco-based products for E_{vmax} and T_{Evmax} in the subjective parameter "satisfaction", measured using a 100 mm VAS after IP use.
		4d.	PD (subjective outcome parameters): The difference between the three NP products and the two tobacco-based products for the subjective parameters "product-liking" and "intent to use again", measured using a 100 mm VAS 30 min after IP use.
5.	To evaluate the safety and tolerability of the three NP products and the two tobacco-based products by administering single doses in current, daily oral tobacco/NP users.	5.	Frequency, intensity, and seriousness of AEs.

No.	Exploratory objectives	No.	Endpoints
1.	To evaluate the impact on "product-liking" *vs*. the subjects' usual oral tobacco/nicotine product of choice by administering single doses of the three NP products and the two tobacco-based products.	1.	The difference in "product-liking" *vs*. the subjects' usual oral tobacco/nicotine product of choice between the three NP products and the two tobacco-based products measured on a 3-point scale using a MCQ 30 min after IP use.
2.	To compare the nicotine extraction normalized PK parameters, specifically the AUC_{0-inf} and C_{max}, between the three NP products and the two tobacco-based products.	2.	The difference in nicotine extraction normalized AUC_{0-inf} and C_{max} between the three NP products and the two tobacco-based products.

AE=adverse event, AUC=area under the plasma concentration vs. time curve, AUC_{0-inf}= AUC from 0 to infinity, AUC_{0-last}= AUC from 0 to time of last measurable plasma concentration, $AUC_{0-1.5h}$= AUC from time 0 to time 1.5 hours, CI=confidence interval, C_{max}=maximum observed concentration, E_{dmax}=largest decrease from baseline, E_{imax}=highest increase from baseline, $E_{max0-60}$=E_{max} from time 0 to 60 min, E_{vmax}= largest value, IP=investigational product, MCQ=Multiple choice question, NP=nicotine pouch, PD=pharmacodynamic, PK=pharmacokinetic, T_{Edmax}=time to the first instance of E_{dmax}, T_{Eimax}= time to E_{imax}, $T_{Emax0-60}$=time to $E_{max0-60}$, T_{max}=time of occurrence of C_{max}, T_{Evmax}= time to the first instance of E_{vmax}, VAS=visual analog scale.

Number of subjects planned

Approximately 76 subjects are planned to be screened to achieve 43 randomized subjects and at least 38 evaluable subjects, *i.e.*, subjects who have received all five IPs and have reliable C_{max} values for all IPs.

An effort will be made to ensure at least 17 of the randomized subjects (approximately 40%) are female. However, a minimum of 9 female subjects (approximately 20%) will be considered acceptable.

Diagnosis and main eligibility criteria

Healthy male or female subjects aged ≥21 to ≤60 years may be considered for participation in the study. These subjects should have used oral tobacco/NP products for ≥1 year and have a minimum daily consumption of five pouches. Furthermore, they should be willing and able to use both tobacco-based products and NPs. 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 subjects 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 the clinic for a screening visit followed by five IP use visits (Visits 2-6) on separate days.

The screening visit (*Visit 1*) will take place within 4 weeks prior to the start of Visit 2 and will include an eligibility check, including evaluations of smoking and oral tobacco/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.

Prior to each IP use visit (Visit 2-6), subjects will abstain from tobacco/nicotine products as well as smoking (cigarettes or e-cigarettes) for >12 h. All treatment sessions will be performed during the morning hours (08:00 to 12:00) to facilitate abstinence.

At Visit 2 (Day 1), eligible subjects will return to the study site. The IPs will be administered as single pouches in a pre-determined randomized order. Subjects will keep the pouch still between the upper lip and gum for 30 min and will be instructed not to manipulate the pouch with the tongue or lips. They will also be instructed not to eat, drink, chew gum, or brush their teeth for 30 min before, during, and 30 min after IP use.

After 30 min, each used pouch will be collected and frozen (-20°C) pending analysis of residual nicotine content. Unused pouches from the same batch will serve as references and will be stored at - 20°C pending analyses.

Blood samples for the assessment of nicotine plasma levels and PK parameters will be collected at pre-defined time points from pre-use to 6 h after each IP use. The PD effects of the IPs will be determined using pulse rate measurements and subjective parameters (using VAS questions) at the same pre-defined time points as well as an MCQ 30 min after IP use.

AEs will be collected through subject interviews and will also include any AEs reported spontaneously by the subjects, starting from the initiation of IP use, and continuing until the last IP use visit (Visit 6).

Visits 3 to 6 will follow the same schedule as Visit 2. Each visit will be scheduled on separate days, preferably with at least 24 h between visits. However, it is acceptable to have visits on consecutive days, as long as all visits are not scheduled consecutively.

Investigational products and dosage

IPs	Nicotine content per pouch
NP 1 –Dry, flavor A	3 mg
NP 2 – Moist, flavor B	3 mg
NP 3 – Moist, unflavored	3 mg
T1 – Tobacco-based snus 1	4 mg
T2 – Tobacco-based snus 2	8 mg

Duration of investigational product use

The participating subjects will receive IPs on five occasions, in a cross-over fashion, with 30 min 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 3 weeks, not including the preceding 4-week screening period.

Pharmacokinetic assessments

Blood samples for analysis of PK parameters will be collected pre-use, and at 5 min, 10 min, 15 min, 20 min, 30 min, 40 min, 60 min, 1 h:30 min, 2 h, 4 h, and 6 h post-use. The PK parameters in the study will include $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}1.5h}$, C_{max}, T_{max}, and $T_{1/2}$.

Pharmacodynamic assessments

The PD effects will be assessed by measuring pulse rate and subjective parameters (using VAS) from pre-use (10 min prior to IP use) to 6 h post-use, at pre-defined time points. The subjective parameters that will be assessed are "craving", "satisfaction", "product-liking", and "intent to use again". In addition, "product-liking" *vs*. the subjects' usual oral tobacco/nicotine product of choice will be assessed using a 3-point scale questionnaire at 30 min post-use.

Nicotine extraction assessment

Used pouches will be collected after 30 min of use for the determination of residual nicotine in the IPs. The extracted amount (mg/unit) and extracted fraction (%) of nicotine will be assessed.

Safety assessments

AEs will be collected through subject interviews and will also include any AEs reported spontaneously by the subjects, starting from the initiation of IP use (Visit 2) and continuing until the last IP use visit (Visit 6).

Statistical methods

Using a coefficient of variation (CV) of 35%, based on previous studies, a power of 80%, a significance level of 10%, and lower and upper equivalence bounds of 0.8 and 1.25, with a null ratio of 1, 38 evaluable subjects will be needed. Assuming a dropout rate of 10%, a total of 43 subjects will be randomized.

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 statistical analysis software (SAS) Version 9.4 or later (SAS Institute, Inc., Cary, NC).

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

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 intake of IP and end time as 23:59, resulting in the longest possible treatment-emergent duration of the AE.

No adjustment for multiple comparisons will be made. All formal comparisons will be made toward a designated reference product, and all significant findings will be reviewed for medical relevance. Spurious data will be evaluated continuously through data validation and, if connected to protocol deviations, evaluated case-by-case at the latest prior to the declaration of clean file and database lock.

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

Methods for handling missing, unused, and spurious data will be further specified 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	Explanation
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 0 to infinity
$AUC_{0\text{-last}}$	AUC from 0 to time of last measurable plasma concentration
$AUC_{0\text{-}1.5h}$	AUC from time 0 to time 1.5 hours
BMI	Body mass index
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
$E_{max0\text{-}60}$	E_{max} from 0 to 60 minutes
EU	European Union
E_{vmax}	Largest value
FAS	Full analysis set
FDA	The United States Food and Drug Administration
GCP	Good clinical practice
GDPR	General data protection regulation
HIV	Human immunodeficiency virus
HR	Heart rate

Abbreviation	Explanation
ICF	Informed consent form
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
MCQ	Multiple-choice question
MedDRA	Medical dictionary for regulatory activities
NP	Nicotine pouch
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PKAS	PK analysis set
PT	Preferred term
QC	Quality control
RBM	Risk based monitoring
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
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}
$T_{Emax0-60}$	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

Abbreviation	Explanation
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 (PI) 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]

Clinical conduct

Site 1:

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

Coordinating/Principal Investigator (Site 1)

[redacted]

Site 2:

CTC GoCo
Vetenskapens gränd 11
SE-431 53 Mölndal, Sweden

Principal Investigator (Site 2)

[redacted]

Study management

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

Clinical Research Manager

[redacted]

Biostatistician

[redacted]

Pharmacokineticist

[redacted]

Medical Writer

[redacted]

Laboratory (virology)

[redacted]

Laboratory (bioanalysis)	[redacted]
Laboratory (extraction)	Regulatory & Scientific Affairs [redacted]
Investigational product (IP) manufacturing	[redacted]
IP packaging and labeling	[redacted]
Electronic data capture (EDC) system provider	[redacted]

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 cannot or 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.

Use of oral tobacco 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 the substance that majorly contributes to the addictive properties of tobacco products. Nicotine exposure may contribute to adverse pregnancy outcomes. 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 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 currently common in Scandinavia and the US, with contents up to 20 mg/unit or more.

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.

To evaluate the abuse liability potential of different formats of NPs in comparison to commercially available tobacco-based traditional snus products, pharmacokinetic/pharmacodynamic (PK/PD) studies are crucial.

6.2 Study rationale

The study aims to compare nicotine exposure from NP products to that from tobacco-based products, which will have varying strengths, formats and flavors. The goal is to identify one tobacco-based product for each NP product that has a comparable maximum plasma concentration (C_{max}). This will allow for fair and accurate comparisons regarding abuse liability potential in compliance with the US Food and Drug Administration (FDA) guidelines on applications for tobacco and nicotine products. The rationale for the study design is presented in Section 8.2.

6.3 Risk/benefit assessment

6.3.1 Risk assessment

All research subjects must be daily Swedish snus and/or NP users for at least 1 year, consuming at least five pouches per day. They must be willing and able to use both NPs and tobacco-based products. 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 administrations of two moist NP products (both 3 mg), one dry NP product (3 mg), and two tobacco-based snus products (4 mg and 8 mg). All IPs are of regular nicotine strength and there are commercially available products with higher nicotine content on the market. Subjects must abstain from tobacco/nicotine products for at least 12 h before use and will only be administered one product during each of the study visits. Therefore, it is reasonable to anticipate that daily nicotine exposure will be lower during these 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 or cardiovascular disease or other medical condition who may be particularly vulnerable to nicotine exposure, are 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*.). Aside from nicotine, all ingredients used in the NP products are approved for use in food.

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 PIs at the study sites 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 reactions 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.*, 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. The repeated blood sampling for PK analysis will be conducted during a 3-week period to give sufficient time between each blood sample occasion. Study-specific evaluations and sampling procedures, such as blood pressure measurements using a blood pressure cuff (at screening) and frequent blood sampling (during Visits 2-6), may cause transient discomfort. However, the risk is deemed to be low and ethically justifiable. Overall, the combined safety data from previous pre-clinical and clinical studies have not revealed any safety issues that would outweigh the expected benefits of the study.

6.3.2 Benefit assessment

In analogy with a regular phase I study 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

The long-term health risks of NPs are not known. Since they contain fewer harmful substances than tobacco-based products, as they do not contain tobacco, the extensive research available for tobacco-based snus can be used to estimate the long-term health risks of NPs, provided that the nicotine exposure from NPs is not higher than from tobacco-based snus.

The overarching aim of the study is to compare nicotine exposure from NP products to that from tobacco-based products, which will have varying nicotine strengths, formats, and flavors. The goal is to ensure that each tested format of the NP products has a similar nicotine delivery profile, measured as C_{max}, to an existing commercially available tobacco-based snus product. This will allow for fair and accurate comparisons regarding potential abuse liability in compliance with FDA guidelines on applications for tobacco and nicotine products, supporting a potential application to the FDA for market authorization.

As mentioned above, subjects must abstain from tobacco/nicotine products for at least 12 h before use and will only be administered one product during study visits. Furthermore, all IPs are of regular nicotine strength (3 mg to 8 mg). Therefore, it is reasonable to anticipate that daily nicotine exposure will be lower during these visits.

The potential AEs and risks associated with the study procedures are likely to be minor and/or clinically insignificant. It is concluded that the planned study assessments suffice to meet the scientific and medical goals. Therefore, the potential benefits of the study outweigh the potential risks for the daily habitual tobacco-based snus and/or NP users who will participate in this study.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary objectives and endpoints

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

Table 7.1-1 Primary study objective and endpoint

Primary objective	Endpoint	Assessments	Analysis
To demonstrate the similarity in C_{max} between each of the three NP products and at least one of the two tobacco-based products.	Similarity in baseline-adjusted C_{max} based on nicotine plasma concentrations after administering single doses of the three NP products and the two tobacco-based products.	Nicotine plasma concentration analysis (Section 11.3.1)	See Section 17.6.1

C_{max}=maximum observed concentration, NP=nicotine pouch

7.2 Secondary objective and endpoints

The secondary study objectives and endpoints are presented in Table 7.2-1.

Table 7.2-1 Secondary objectives and endpoints

No.	Secondary objectives	No.	Endpoints	Assessments	Analysis
1.	To demonstrate equivalence in C_{max} and $AUC_{0\text{-}inf}$ between each of the three NP products and at least one of the two tobacco-based products.	1.	Equivalence (90% CI for the ratio between 0.8 and 1.25) in baseline-adjusted C_{max} and $AUC_{0\text{-}inf}$ based on nicotine plasma concentrations after administering single doses of the three NP products and the two tobacco-based products.	Nicotine plasma concentration analysis (Section 11.4.1)	See Section 17.7.1
2.	To compare the *in vivo* extracted amount (mg/unit) and extracted fraction (%) of nicotine from the three NP products with those from the two tobacco-based products.	2.	The difference in *in vivo* extracted amount (mg/unit) and extracted fraction (%) of nicotine between the three NP products and the two tobacco-based products.	Extracted amount of nicotine (Section 11.4.2)	See Section 17.7.2
3.	To compare the PK profile between the three NP products and the two tobacco-based products.	3.	The difference between the three NP products and the two tobacco-based products in the non-adjusted and baseline-adjusted PK parameters: $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $AUC_{0\text{-}1.5h}$, $AUC_{0\text{-}last}$, and $T_{½}$.	PK blood sampling and analysis (Section 11.4.1)	See Section 17.7.3
4.	To assess the PD effects, measured as pulse rate and subjective outcome measures, of the three NP products and the two tobacco-based products.	4a.	PD (pulse rate): The difference between the three NP products and the two tobacco-based products for E_{imax}, T_{Eimax}, $E_{max0\text{-}60}$, and $T_{Emax0\text{-}60}$ in pulse rate, measured using a pulse oximeter after IP use.	Pulse rate evaluation (Section 11.4.3.1)	See Section 17.7.4
		4b.	PD parameters: The difference between the three NP products and the two tobacco-based products for E_{dmax} T_{Edmax} in the subjective parameter	Subjective outcome evaluation (Section 11.4.3.2)	See Section 17.7.4

			"craving", measured using a 100 mm VAS after IP use.		
		4c.	PD parameters: The difference between the three NP products and the two tobacco-based products for E_{vmax} and T_{Evmax} in the subjective parameter "satisfaction", measured using a 100 mm VAS after IP use.	Subjective outcome evaluation (Section 11.4.3.2)	See Section 17.7.4
		4d.	PD (subjective outcome parameters): The difference between the three NP products and the two tobacco-based products for the subjective parameters "product-liking" and "intent to use again", measured using a 100 mm VAS 30 min after IP use.	Subjective outcome evaluation (Section 11.4.3.2)	See Section 17.7.4
5.	To evaluate the safety and tolerability of the three NP products and the two tobacco-based products by administering single doses in current, daily oral tobacco/NP users.	5.	Frequency, intensity, and seriousness of AEs.	AE reporting (Section 11.4.4)	See Section 17.7.5

AE=adverse event, AUC=area under the plasma concentration *vs.* time curve, $AUC_{0\text{-inf}}$= AUC from 0 to infinity, $AUC_{0\text{-last}}$= AUC from 0 to time of last measurable plasma concentration, $AUC_{0\text{-1.5h}}$= AUC from time 0 to time 1.5 hours, CI=confidence interval, C_{max}=maximum observed concentration, E_{dmax}=largest decrease from baseline, E_{imax}=highest increase from baseline, E_{vmax}= largest value, IP=investigational product, NP=nicotine pouch, PD=pharmacodynamic, PK=pharmacokinetic, T_{Edmax}=time to the first instance of E_{dmax}, T_{Eimax}= time to the first instance of E_{imax}, T_{max}=time of occurrence of C_{max}, T_{Evmax}= time to the first instance of E_{vmax}, VAS=visual analog scale

7.3 Exploratory study objectives and endpoints

The exploratory study objectives and endpoints are presented in Table 7.3-1.

Table 7.3-1 Exploratory study objectives and endpoints

No.	Exploratory objectives	No.	Endpoints	Assessments	Analysis
1.	To evaluate the impact on "product-liking" *vs*. the subjects' usual oral tobacco/nicotine product of choice by administering single doses of the three NP products and the two tobacco-based products.	1.	The difference in "product-liking" *vs*. the subjects' usual oral tobacco/nicotine product of choice between the three NP products and the two tobacco-based products measured on a 3-point scale using an MCQ 30 min after IP use	Subjective outcome evaluation (Section 11.5.1.1)	See Section 17.8.1.
2.	To compare the nicotine extraction normalized PK parameters, specifically the $AUC_{0\text{-}inf}$ and C_{max}, between the three NP products and the two tobacco-based products.	2.	The difference in nicotine extraction normalized $AUC_{0\text{-}inf}$ and C_{max} between the three NP products and the two tobacco-based products.	Nicotine extraction from pouches (Section 11.4.2)	See Section 17.8.2.

$AUC_{0\text{-}inf}$= AUC from 0 to infinity, C_{max}=maximum observed concentration, NP=nicotine pouch, MCQ=multiple-choice question, PK=pharmacokinetic

8 STUDY DESIGN

8.1 Overall study design and schedule of events

This is a multi-center, open-label, randomized, 5-way cross-over, single-dose administration study in healthy male and female volunteers. The IPs include two flavored NP products (both 3 mg), one unflavored NP product (3 mg), and two tobacco-based snus products (4 mg and 8 mg).

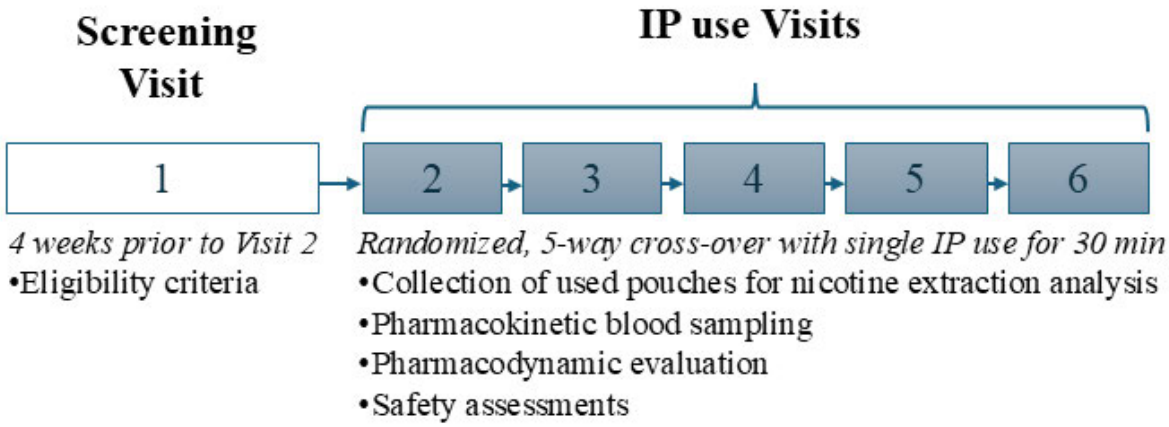
The study will randomize 43 subjects to attain at least 38 evaluable subjects. An evaluable subject is defined as one with reliable C_{max} values for all five IPs.

The subjects will be healthy male and female subjects who have used oral tobacco/NP products for ≥1 year, with a minimum daily consumption of five pouches. Efforts will be made to include at least 17 female subjects (approximately 40%). However, a minimum of 9 female subjects (approximately 20%) will be considered acceptable.

Each subject will participate in the study for approximately 3 weeks, not including the preceding up to 4-week screening period.

An overview of the study design is shown in Figure 8.1-1. An overall schedule of events is presented in Table 8.1-1 and a detailed schedule of events for each IP use visit is presented in Table 8.1-2. Study assessments are described in Section 11.

Figure 8.1-1 Overview of the study design



The screening visit (*Visit 1*) will take place within 4 weeks prior to Visit 2 and will include an eligibility check, including evaluations of smoking and oral tobacco/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.

At Visit 2, the subjects will return to the study site for the first IP use visit.

Subjects shall abstain from tobacco/nicotine products as well as smoking (cigarettes or e-cigarettes) for 12 h prior to each IP use visit (Visits 2 to 6). 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. Randomization will take place before the first IP use. Subjects will keep the pouch between their upper lip and gum for 30 min and will be instructed not to manipulate the pouch with the tongue or lips. They will be instructed not to eat, drink, chew gum, or brush their teeth for 30 min before, during use, and 30 min after the IP use. After 30 min, each used pouch will be collected and frozen (-20°C) pending analysis of residual nicotine content. Unused pouches from the same batch will serve as references and will be stored at -20°C pending analyses.

Blood samples for the assessment of nicotine plasma levels and PK parameters will be collected at pre-defined time points from pre-use to 6 h after each IP use. The PD effects of the IPs will be determined using pulse rate measurements and subjective parameters (using VAS questions) at the same pre-defined time points as well as a multiple-choice question (MCQ) 30 min after IP use.

AEs will be collected through subject interviews and will also include any AEs reported spontaneously by the subjects, starting from the initiation of IP use (Visit 2), and continuing until the last IP use visit (Visit 6).

Visits 3 to 6 will follow the same schedule as Visit 2. Each visit will be scheduled on separate days, preferably with at least 24 h between visits. However, it is acceptable to have visits on consecutive days, as long as all IP use visits are not scheduled consecutively.

Table 8.1-1 Overall schedule of events

Events	CSP section	Visit 1 Screening	Visit 2	Visit 3-6
Informed consent	11.2.1	X		
Demographics	11.2.2	X		
Medical/surgical history	11.2.3	X		
History of and current nicotine product use	11.2.4	X		
Inclusion/exclusion criteria	9.4/9.5	X	X[1]	
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	11.2.9	X		
HIV, Hepatitis B and C	11.2.10	X		
Pregnancy test[2]	11.2.11	X	X	X[3]
Drug screen[4]	11.2.12	X	X	
Alcohol screen[4]	11.2.13	X	X	
Randomization	9.9		X	
IP (pouch) administration	10.5		X[5]	X[5]
PK blood sampling (plasma)	11.3.1		X[5]	X[5]
Subjective effects (VAS questions and MCQ)	11.4.3.2 11.5.1.1		X[5]	X[5]
Pulse rate (pulse oximeter)	11.4.3.1		X[5]	X[5]
IP (pouch) collection	11.4.2		X[5]	X[5]
Baseline symptoms	11.2.14	X	X	
AEs	11.4.4		X	X
Prior and concomitant medications	11.2.15	X	X	X

AE=adverse event, BMI= body mass index, HIV=human immunodeficiency virus, IP=investigational product, MCQ=multiple-choice question, VAS=visual analog scale.

1. Confirmation of eligibility criteria.
2. Only subjects of childbearing potential.
3. Only at the discretion of the Investigator on Visits 3-6.
4. Additional drug and alcohol tests may be performed at the discretion of the Investigator during IP use visits.
5. The detailed timing of assessments is outlined in Table 8.1-2.

Table 8.1-2 Detailed schedule of events for each IP use visit (Visits 2-6)

Visits 2-6																
Assessment / Time point	**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	X[1]															
Drug screen	X[2]															
Alcohol screen	X[2]															
Pregnancy test	X[3]															
Randomization	X[4]															
IP (pouch) administration					X											
IP (pouch) collection										X						
PK blood sampling (plasma)			X[5]			X	X	X	X	X	X	X	X	X	X	X
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 ("product-liking" *vs.* usual product)										X						
Pulse rate (pulse oximeter)		X				X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Baseline symptoms		X[7]														
AEs					X[8]											
Prior and concomitant medications	X															

1. Only at Visit 2. Confirmation of eligibility before randomization.
2. Only at Visit 2. Additional drug and alcohol tests may be performed during IP use visits at the discretion of the Investigator.
3. Only subjects of childbearing potential. Additional tests at the discretion of the Investigator on Visits 3-6.
4. Randomization occurs only on Visit 2.
5. Pre-use PK-sample taken at any time within -10 min to -1 min prior to IP use.
6. The minute prior to the PK sample.
7. Only on Visit 2. Baseline symptoms experienced prior to first IP use.
8. AEs experienced from first IP use until the last IP use (Visits 2-6).

8.2 Rationale for study design

This is a multi-center, open-label, randomized, 5-way cross-over, single-dose administration study aiming to identify at least one tobacco-based snus product for each of the three NP products with comparable C_{max}. Two tobacco-based products with a regular nicotine content, 4 mg and 8 mg, were selected. This variation is anticipated to ensure equivalence in C_{max} between the tobacco-based snus and NP products.

A cross-over design was chosen to yield a more efficient evaluation of IPs than a parallel study design, *i.e.*, fewer subjects are required since each subject will serve as its own control. To avoid carry-over effects, subjects will abstain from oral tobacco/nicotine products as well as smoking (cigarettes or e-cigarettes) for at least 12 h prior to 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 76 subjects are planned to be screened with the aim of randomizing at least 43 subjects and achieving 38 evaluable subjects.

Efforts will be made to include at least 17 female subjects (approximately 40%). However, a minimum of 9 female subjects (approximately 20%) 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. Willing and able to give written informed consent for participation in the study.
2. Subjects who have used Swedish snus and/or NP products for ≥1 year, with a minimum daily consumption of five pouches, and who are willing and able to use both oral tobacco-based and NP products while abstaining from other tobacco/nicotine products during the study.
3. Healthy male or female subjects aged 21 to 60 years, inclusive.
4. Medically healthy subject without abnormal clinically significant medical history, physical findings, vital signs, ECG, and hepatitis B/C and human immunodeficiency virus (HIV) results 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 is their consistent practice) or agree to use a highly effective method of contraception with a failure rate of <1% to prevent pregnancy for the duration of the study.

   The following are considered highly effective methods of contraception:

   - 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),
   - 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 ongoing manifestations of hypertension or any cardiovascular disease as judged by the Investigator.
2. Any surgical or medical condition, including abnormal salivation (also 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 because of participation in the study, influence the results, or the subject's ability to participate in the study.
3. A history of diagnosed severe allergy/hypersensitivity or ongoing manifestations of severe allergy/hypersensitivity to aroma compounds (including fragrances and/or flavorings), as judged by the Investigator.
4. Subjects with poor venous access or being scared of needles.
5. Any planned major surgery within the duration of the study.
6. Subjects who are pregnant, currently breastfeeding, or intend to become pregnant during the course of the study.
7. Any positive result at the screening visit for serum hepatitis B surface antigen, hepatitis B and C antibodies, and/or HIV.
8. Positive result for drugs of abuse or alcohol at the screening visit or on admission to the study site prior to IP use. Positive results that are expected given the subject's medical history and prescribed medications can be disregarded as judged by the Investigator.
9. History of alcohol abuse or excessive intake of alcohol, 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 attention deficit hyperactivity disorder (ADHD) medications, including *pro re nata* (as needed) use.
13. Plasma donation within 1 month of screening or blood donation (or corresponding blood loss) until 3 months after the last IP use visit.

14. Subjects who intend to change their nicotine consumption habit, including the intention 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.

9.6.1 General restrictions

1. Contraception requirements: Subjects of childbearing potential are expected to use contraceptive methods in accordance with inclusion criterion #5 or practice abstinence from heterosexual intercourse (if this is their consistent practice) during the clinical study.
2. Tobacco/nicotine products:

   Subjects shall abstain from any self-administered oral tobacco/nicotine products as well as smoking (cigarettes and e-cigarettes) for at least 12 hours prior to IP use visits and during each IP use visit (Visits 2-6).
3. Mouth-related procedures: Subjects shall abstain from eating, drinking, or conducting any other mouth-related procedure (*e.g.*, tooth brushing) for 30 min prior to IP use, during IP use, and for 30 min after IP removal (Visits 2-6).
4. Drugs of abuse: Subjects shall abstain from any drugs of abuse during the study.
5. Alcohol: Subjects shall abstain from alcohol for at least 12 h prior to each visit from Visit 2 to the last visit (Visits 6).
6. Blood donation: The subjects must not donate blood or plasma within 1 month of screening until 3 months after the last IP use visit (Visit 6).
7. Participation in other clinical studies: The subjects are not allowed to participate in any other clinical study from the screening visit (Visit 1) until the last visit (Visit 6).

9.6.2 Prior and concomitant therapy

Use of any prescribed medication that includes beta-adrenergic blocking agents (beta blockers) or ADHD medications, including *pro re nata* use, is not allowed from the screening visit (Visit 1) until the last visit (Visit 6). As outlined in exclusion criterion #12, subjects currently using beta-adrenergic blocking agents or ADHD medications will be excluded from participation in the study.

There will be no other restrictions concerning concomitant medications or therapies, as long as the subject is on a stable course of medication from the screening visit to the last IP use visit (Visit 6). Prescribed medications taken *pro re nata* may be a reason for exclusion as judged by the Investigator if they affect the subject's general condition and salivation.

As detailed in exclusion criterion # 8, a positive drug screen will exclude a subject from participation in the study. However, positive results that are expected given the subject's medical history and prescribed medications (*e.g.*, opioid analgesics) can be disregarded as judged by the Investigator.

9.7 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical study but do not fulfill all eligibility criteria and are not subsequently included in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects. Minimal information includes documentation of signed and dated informed consent form (ICF) and reason(s) for screening failure.

Re-screening can 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 subjects.

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

9.8 Subject withdrawal

9.8.1 General withdrawal criteria

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

Subjects may be discontinued 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 prematurely discontinues participation in 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 primary reason for discontinuation/early withdrawal must be specified in the eCRF and final drug accountability must be performed. If the reason for discontinuation was an AE, the AE must be specified 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 10 use sequences using a Latin squares William's design balancing for first-order carry-over effects. The following sequences will be randomized:

Sequence 1: A B E C D
Sequence 2: B C A D E
Sequence 3: C D B E A
Sequence 4: D E C A B
Sequence 5: E A D B C
Sequence 6: D C E B A
Sequence 7: E D A C B
Sequence 8: A E B D C
Sequence 9: B A C E D
Sequence 10: C B D A E

where

A = NP 1 – Dry, flavor A – 3 mg
B = NP 2 – Moist, flavor B – 3 mg
C = NP 3 – Moist, unflavored – 3 mg
D = T1 – Tobacco-based snus 1 – 4 mg
E = T2 – Tobacco-based snus 2 – 8 mg

As this is an open-label study, the IP use sequence to which each subject is allocated will be recorded in the eCRF. Computer-generated randomization lists for each site will be created using the statistical analysis software (SAS) Proc Plan, SAS Version 9.4. The randomization lists will contain the site, subject number, randomization sequence, visit, and product.

The randomization list will be generated by CTC. The original randomization list will be kept by the randomizer and copies of the randomization list will be provided to each site and to the IP packing company.

10 INVESTIGATIONAL PRODUCTS

The IPs are supplied by Swedish Match.

10.1 Identity of investigational products

The IPs that will be used in the study are detailed in Table 10.1-1.

Table 10.1-1 Identity of investigational products and nicotine contents

IP	Nicotine content per pouch
NP 1 – Dry, flavor A	3 mg
NP 2 – Moist, flavor B	3 mg
NP 3 – Moist, unflavored	3 mg
T1 – Tobacco-based snus 1	4 mg
T2 – Tobacco-based snus 2	8 mg

10.2 Manufacturing, packaging, and labeling

All IPs are manufactured and packaged by Swedish Match in compliance with the Swedish law on food production. Production sites and batch IDs for the IPs will be documented in the trial master file (TMF).

IPs will be transferred from the original container, weighed, and individually packaged in identical sealed food-approved test containers at the Swedish Match analytical laboratory. The containers will be labeled with unique identification numbers by Swedish Match in accordance with the randomization lists. IPs will be shipped by Swedish Match directly to CTC.

10.3 Conditions for storage

All moist IPs (the two NP moist 3 mg products and the two tobacco-based products) will be stored under refrigerator temperature (4-8°C), while the dry IP (NP dry 3 mg product) will be stored in room temperature, both in access-controlled storage areas.

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, as well as 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 of each IP use visit (Visits 2-6). Subjects will keep the pouch between their upper lip and gum for 30 min and will be instructed not to manipulate the pouch with the tongue or lips. They will be instructed not to eat, drink, chew gum, or brush their teeth for 30 min before, during use, and 30 min after the use of IP.

Subjects shall abstain from oral tobacco/nicotine products as well as smoking (cigarettes or e-cigarettes) for at least 12 h prior to each IP use visit. To this end, subjects will be instructed to abstain from such products from approximately 20:00 (8 pm) the day before IP use visits (Visits 2-6). All IP uses will be performed during the morning hours (08:00 to 12:00) to facilitate abstinence.

10.6 Investigational product final accountability

Any IP not used, as well as all empty containers will be destructed 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 is adequately destroyed and documented.

11 STUDY ASSESSMENTS

The study assessments are described in the sections below and the timing of assessments are detailed in the schedule of events (Table 8.1-1 and Table 8.1-2).

11.1 Recording of data

The PIs 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 sampling occurs as close as possible to the scheduled time points in Table 8.1-2. In order to achieve this, the timing priority order at a particular time point is:

1. Blood samples for PK
2. Pulse rate assessment
3. Visual analog scale (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 oximeter)	VAS questions "craving" and "satisfaction"	VAS questions "product-liking" and "intent to use again"	MCQ
-00:15			± 5 min			
-00:10		Pre-use sample can be taken at any time within 10 min prior to IP use.		± 3 min[2]		
-00:01						
00:00	± 0 min (IP admin.)					
00:05		± 2 min	± 2 min[1]	± 3 min		
00:10		± 2 min	± 2 min[1]	± 3 min		
00:15		± 2 min	± 2 min[1]	± 3 min		
00:20		± 2 min	± 2 min[1]	± 3 min		
00:30	±1 min (IP collection)	± 5 min	± 5 min[1]	± 5 min	± 10 min	± 10 min
00:40		± 5 min	± 5 min[1]	± 5 min		
01:00		± 10 min	± 10 min[1]	± 10 min		
01:30		± 10 min	± 10 min[1]	± 10 min		
02:00		± 10 min	± 10 min[1]	± 10 min		
04:00		± 10 min	± 10 min[1]	± 10 min		
06:00		± 10 min	± 10 min[1]	± 10 min		

1. Pulse rate should be measured prior to PK blood sampling if possible.
2. Only "craving" at -10 min.

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: gender, age, ethnicity, and race.

11.2.3 Medical/surgical history

Medical/surgical history will be obtained by subject interview to verify that the eligibility criteria are met.

11.2.4 History of nicotine use

History of oral tobacco/nicotine products use in terms of brands, average consumption per day during the last 30 days, duration of use (years, months), history of smoking in terms of number of cigarettes per day during the last 30 days, as well as history of vaping in terms of number of days during last 30 days, will be obtained by subject interview.

11.2.5 Eligibility criteria

Eligibility criteria should be checked during screening and verified before randomization and use of the first IP on Visit 2. The criteria are specified in Sections 9.4 and 9.5.

11.2.6 Height, weight, and body mass index

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 include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities.

11.2.8 Vital signs

Systolic and diastolic blood pressure and pulse will be measured at screening in a supine position after 10 min 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 2-6): 40 to 100 bpm. Refer to Section 11.4.3.1.

11.2.9 Electrocardiogram

Single 12-lead ECGs will be recorded at the screening in a supine position after 10 min of rest using an ECG machine. The resting HR 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 B and 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 females of childbearing potential will undergo a urine dipstick pregnancy test at the screening visit and at visits specified in Table 8.1-1. At Visits 3 to 6, pregnancy tests will be conducted only at the discretion of the Investigator.

11.2.12 Drug screen

Urine will be screened for drugs of abuse at time points outlined in the schedule of events (Table 8.1-1) using the Drug Screen Multi-15 Dip Test. Additional random tests may be conducted during the study period at the discretion of the Investigator.

11.2.13 Alcohol test

Urine alcohol tests will be performed at the time points outlined in the schedule of events (Table 8.1-1 and Table 8.1-2). Additional random tests may be conducted during the study period 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 medication

Prior medications taken within 2 weeks prior to screening 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 (prior to IP use), 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, 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 6) 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 primary endpoints

11.3.1 Nicotine plasma concentration and pharmacokinetic sampling and analysis

Venous blood samples (approximately 3 mL) for the determination of plasma concentrations of nicotine after IP use will be collected through an indwelling venous catheter at the pre-specified visits and time points detailed in Table 8.1-2. It is important that blood PK sampling does not deviate from the planned time points more than the allowed time deviations, as outlined in Table 11.1-1.

Pre-PK sampling should be conducted -10 min to -1 min 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 min at 20°C (± 4°C) to separate the plasma within 60 min from when the sample was drawn. The separated plasma from each blood sample will be divided into 2 aliquots in pre-labeled cryotubes and frozen at -80°C within 1 h 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 Pharmacokinetic sampling related to secondary endpoints

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

11.4.2 Nicotine extraction from pouches

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

All the collected pouches will be frozen within 60 min at -20°C. Pouches for extraction of nicotine will be analyzed by Swedish Match.

All pouches will be weighed prior to use, as will reference pouches (will be done by the Sponsor prior to shipment to site).

11.4.3 Pharmacodynamic effects

The PD effects of the IPs will be assessed by measuring pulse rate and subjective parameters (using VAS and MCQ) at pre-defined time points as described below and in Table 8.1-2.

11.4.3.1 Pulse rate

The pulse rate will be monitored using a pulse oximeter and will be spot-assessed at -15 min pre-use, as well as at the minute prior to the PK sample taken at 5 min, 10 min, 15 min, 20 min, 30 min, 40 min, 60 min, 1 h:30 min, 2 h, 4 h, and 6 h post-use (see Table 8.1-2).

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 parameters

Subjective parameters (“craving”, “satisfaction”, “product-liking”, and “intent to use again”) will be rated using 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 min prior to IP use, and 5 min, 10 min, 15 min, 20 min, 30 min, 40 min, 60 min, 1 h:30 min, 2 h, 4 h, and 6 h post-use.

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

In addition, “product-liking” and “intent to use again” parameters will be assessed at 30 min 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 8.1-2 and allowed deviations from actual time are outlined in Table 11.1-1.

11.4.4 Adverse events

The PIs are responsible for ensuring that all medical staff involved in the study 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 well-being 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 2-6).

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 6), 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 based on 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 11.4.4.10.

For the seriousness criteria of inpatient hospitalization or prolongation of existing hospitalization to be fulfilled, inpatient hospitalization is defined as that the participant has been admitted to the hospital for inpatient care, either to the inpatient ward or to the emergency room for observation and/or treatment, that would not have been appropriate in the 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) v5.0 [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 on 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 due to underlying or concurrent illness or 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 h** 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 fill in the SAE form and send it Sponsor or its designee. The study site must notify the site Monitor via 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, within 24 h, be scanned and delivered via encrypted e-mail or secure file transfer to:

A copy of the SAE paper form must also be delivered via encrypted e-mail or secure file transfer to CTC at: [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 to the last visit (Visit 6), whichever comes first. On the last visit, information on new AEs, if any, 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 will not have 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 to the Sponsor all relevant new information 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 regarded as 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 (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up by the Investigator and the Sponsor and documented even after the subject was discontinued from the study.

All pregnancies must immediately be reported by the Investigator to the Sponsor or designee using the Pregnancy Report Form provided in the ISF. Once known, information on the outcome of the pregnancy must also be reported to the Sponsor or designee using the Pregnancy Report Form.

All events of congenital abnormalities, birth defects, and spontaneous miscarriages are SAEs and must be handled and reported as such as described in Section 11.4.4.10.

11.4.4.14 Treatment of overdose

An overdose is a dose in excess of the dose specified for a subject in this clinical study protocol (CSP).

Overdosing is not likely to occur in this study since all IPs will be administered as single doses by site personnel under medical surveillance. In cases of accidental overdose, standard supportive measures will be adopted as required.

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

11.5 Assessments related to exploratory endpoints

11.5.1.1 Exploratory subjective parameters

The subjective parameter "product-liking" *vs*. the subject's usual snus/nicotine product of choice will be assessed at 30 min with the MCQ "How much did you like the product compared with your usual snus or nicotine product of choice?" on a 3-point scale:

"1 = To a lesser extent, 2 = To the same extent, 3 = To a greater extent."

The allowed deviation from the actual time for the MCQ is outlined in Table 11.1-1.

11.5.1.2 Nicotine extraction normalized PK parameters

Nicotine extraction and PK sampling related to exploratory endpoint #2 are part of the procedures described above in Section 11.4.2 and Section 11.3.1, respectively.

11.6 Appropriateness of measurements

All methods used are commonly used 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 until Visit 6 from each subject will be approximately 183.5 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 for persons weighing at least 45-50 kg [12]. Additional blood samples for safety evaluation 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	60	3 mL	180 mL
HIV, Hepatitis B/C	1	3.5 mL	3.5 mL
		Total:	**183.5mL**

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 remains from the laboratory samples will be disposed of after analyses.

The samples for analyses of plasma PK parameters will be stored at ≤ -80 °C until analyzed. The samples will be disposed of after the clinical study report (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 PI will ensure that:

1. Subject withdrawal of consent is notified immediately to the Sponsor.
2. 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 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) guideline [13].

Identified risks will be categorized separately from the CSP.

13.2 Quality assurance and quality control

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

1. Implementing and maintaining quality assurance and quality control (QC) systems with written SOPs with regard to the management of identified risks, CSP compliance, good clinical practice (GCP) compliance, and applicable regulatory requirements.
2. Securing agreements with involved subcontractors and performing regular subcontractor oversight to ensure CSP compliance, GCP compliance, and compliance with applicable regulatory requirements.
3. Implementing a risk-based validated EDC system and maintaining SOPs for the whole life cycle of the system.
4. QC application to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [14] and are consistent with the ICH E6 (R2) guideline for GCP [13], applicable sections of the Clinical Trials Regulation European Union (EU) no.536/2014 [10], and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The coordinating PI is responsible for the submission of the CSP, the subject information and ICF, any other written information to be provided to the subjects, and any advertisements used for recruitment of subjects to applicable IEC for approval.

Approval must be obtained in writing from the IEC before the first subject can be recruited.

The Sponsor will provide the IEC and PI with safety updates/reports according to 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 objectives and the procedures of the study as well as any risks or inconveniences involved. It will be emphasized that participation in the study is voluntary and that the subject may withdraw from participation at any time and for any reason, without any prejudice. All subjects will be given the opportunity to ask questions about the study and will be given 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 the subject and by 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 documentation 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], these pseudonymized data will not identify any persons taking part in the study. If any part of the data is handled by any other organization, inside or outside the EU, appropriate agreements and/or other documentation will be established, to ensure that the data processing

is performed in accordance with the provisions of the GDPR and other relevant legislation before any data transfer takes place.

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 GDPR [15] and the request will be raised to the PIs.

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 by the authorized representatives of the Sponsor.

Personal data that are collected in the study such as health information and ethnicity are considered as 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 AB is the data processor. Any subcontractors used in the study are also data processors.

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

14.5 Changes to the approved clinical study protocol

Any proposed change to the approved final CSP, including appendixes, will be documented in a written and numbered CSP amendment. All substantial amendments to the CSP must be approved by the appropriate IEC before implementation according to applicable regulations.

14.6 Audits and inspections

Authorized representatives of the Sponsor or an IEC may perform audits or inspections at the study site, including source data verification (SDV). The purpose of an audit or inspection is to examine all investigation-related activities and documents systematically and independently, to determine whether these activities were conducted, and whether data were recorded, analyzed, and accurately reported according to the CSP, ICH-GCP guidelines, and any applicable regulatory requirements.

14.7 Insurance

Subjects will be covered under the Sponsor’s liability insurance policy through IF insurance. 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 study 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 Investigator to ensure that all personnel involved in the study 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 Investigator will keep a list of all personnel involved in the study 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/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.

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

- provide information and support to the investigational team,
- confirm that facilities and resources remain acceptable,
- confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals, and regulatory requirements,
- verify that data are being accurately and timely recorded in the eCRFs and that IP accountability checks are being performed,
- verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the RBM plan,
- verify that the correct informed consent procedure has been adhered to for participating subjects,
- 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/destructed accordingly and that this action is documented and reported to the subject,
- verify that AEs are recorded and reported in a timely manner and according to the CSP,
- 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, the Monitor will perform a close-out visit.

15.3 Source data documents

A separate origin of source data list will be generated 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 PI and the Monitor to confirm the agreement before the start of recruitment.

Source documents are all documents used by the Investigator 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 Investigator must guarantee access to source documents to the Monitor, and the IECs, if required.

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 PI and the PI at each site are employees of CTC.

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

The Sponsor and CRO responsibility and duty split is regulated in a separate clinical study agreement. The PIs 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 2025 and to be completed by Q3 2025.

A subject is considered to have completed the study if they have completed all visits in the study including the last visit. The end of the clinical part of the study is defined as the date of the last visit of the last subject in the study.

The end of the study period is defined as the date of the final CSR.

15.6 Termination of the study

The Investigator or the Sponsor may terminate this study prematurely for any reasonable cause. The IEC must be informed promptly. Conditions that may warrant study termination include, but are not limited to, a decision by the Sponsor to suspend or discontinue the development of the IP.

If the study is prematurely terminated or suspended for any reason, the Investigator must promptly inform the study subjects and must ensure appropriate follow-up for the subjects.

15.7 Reporting and publication

15.7.1 Clinical study report

After completion of the study, an ICH E3 [16] guideline-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 PI, 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 PI is responsible for maintaining essential documents, (as defined in ICH E6(R2), Section 8 [13]) for 25 years after the finalization of the CSR. This includes any original source documents 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 as to when these documents no longer need to be retained.

The Sponsor will archive the TMF in accordance with the ICH E6(R2) guideline, Section 8 [13], and applicable regulatory requirements.

The data from the eCRFs will be sent to the Sponsor, and a copy will be sent to the study site and filed in the ISF for archiving for 25 years after the 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 of the eCRF, database setup and management, data entry and verification, data validation, QC 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 documents 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 Investigator will complete data collection. Appropriate training and security measures will be completed with the 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 Investigator or designee. 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 documents 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, Q1-Q3 (interquartile range [IQR]).

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 by non-compartmental analysis using the software Phoenix WinNonlin® version 8.3 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 formal comparisons will be made toward a designated reference product, and all significant findings will be reviewed for medical relevance.

17.1.1 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 intake of IP and end time as 23:59, resulting in the longest possible treatment-emergent duration of the AE.

Spurious data will be evaluated continuously through data validation (see Section 16) and, if connected to protocol deviations, evaluated case-by-case at the latest prior to the declaration of clean file and database lock.

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

Methods for handling of missing, unused, and spurious data will be further specified in the SAP.

17.2 Determination of sample size

The sample size is calculated assuming a 2x2 crossover design analyzed on log scale, using the proposed analysis model outlined under Section 17.7.1. Specifically, the expected model estimates for the equivalence between NP 1 and at least one of the two tobacco-based products are used for the power calculation (Table 17.2-1).

Table 17.2-1 Power calculation

Input	Value	Comment
Power	>80%	Refer to the reasoning presented below this table.
Alpha	10%	Nominally set. Inference is drawn based on a 90% CI.
Hypothesized true geometric least square means ratio	0.95	
Equivalence bounds for the geometric least square means ratio	0.8 to 1.25	
Coefficient of variation	0.35	As observed in previous studies.
Assumed drop-out rate	10%	
Total sample size	**43**	*I.e.,* 43 subjects to be randomized to achieve 38 evaluable subjects for the first secondary endpoint given the assumptions above.

The calculation outlined in Table 17.2-1 above renders an 80% power for one comparison of NP 1 and one of the tobacco-based products. However, as defined in the first secondary objective/endpoint, two comparisons per NP product will be made (one to each of the tobacco-based products) with the understanding that the objective is fulfilled for a specific NP product if equivalence is demonstrated to one of the tobacco-based products.

Let T1 – T2 denote the event that equivalence is found between NP 1 and tobacco products 1 and 2. The probability of demonstrating equivalence between NP 1 and at least one of the tobacco-based products can then be written as:

$$1 - P(\overline{T1}) * P(\overline{T2}|\overline{T1})$$

As evident by this expression, the actual power in the study will be higher than 80%. However, the conditional probabilities of the complement of T2 is unknown, due to its correlation to the preceding comparison. Therefore, the exact power cannot be determined, with the extreme scenarios being completely correlated comparisons resulting in an 80% power and completely uncorrelated comparisons resulting in an 96% power for the study.

Efforts will be made to include at least 17 female subjects (approximately 40%). However, a minimum of 9 female subjects (approximately 20%) will be considered acceptable.

17.3 Analysis data sets

17.3.1 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.

17.3.2 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.

17.4 Pharmacokinetic analysis - general

The PK analysis will be based on the PKAS and performed by CTC. The PK parameters will be calculated by non-compartmental PK analysis using the software Phoenix WinNonlin® version 8.3 or later (Certara Inc., Princeton, NJ, US). In addition to $AUC_{0\text{-}inf}$ and C_{max} parameters, other non-compartmental PK parameters will be determined in relation to secondary endpoints (see Section 17.7.2 below). Where possible, 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, minimum and maximum value. For applicable PK parameters, the geometric mean and CV % will be presented. Categorical data will be presented as counts and percentages, as applicable.

17.5 Description of study population

17.5.1 Demographics and baseline characteristics

Descriptive statistics for demographics, weight, height, BMI, history of oral tobacco/nicotine use, and smoking will be presented for all subjects. All data will be listed by subject number.

17.5.2 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. All data will be listed by subject number.

17.5.3 Investigational product use

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

17.5.4 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.

All data will be listed by subject number.

17.5.5 Vital signs

Vital signs (systolic/diastolic blood pressure, and pulse rate) will be summarized. All data will be listed by subject number.

17.5.6 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.

All data will be listed by subject number.

17.6 Analysis of primary endpoint

17.6.1 Similarity in baseline-adjusted C_{max}

The primary endpoint of this study is to demonstrate the similarity in baseline-adjusted C_{max} based on nicotine plasma concentrations for each of the three NP products and at least one of the two tobacco-based products.

The comparison of C_{max} between the two IPs will be assessed using a mixed model. In this model, the log-transformed C_{max} will be the dependent variable, the product will be the fixed effect, and the participant 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 between a specific NP product and a specific tobacco-based product will be assessed by reviewing the point estimates of the ratios from the model and the descriptive statistics of C_{max} per IP.

17.7 Analysis of secondary endpoints

17.7.1 Equivalence in baseline-adjusted C_{max} and $AUC_{0\text{-}inf}$

C_{max} and $AUC_{0\text{-}inf}$ for each IP will be analysed for baseline-adjusted concentrations using the same model as described in Section 17.6.1.

Equivalence for each of the three NP products and at least one of the tobacco-based products will be concluded if the 90% CI for the ratio of C_{max} and $AUC_{0\text{-}inf}$, respectively, from the model falls within the acceptance interval of 80.00 - 125.00%.

17.7.2 In vivo extracted amount and fraction of nicotine

The difference between 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.

17.7.3 Pharmacokinetics of nicotine in plasma

The following non-compartmental PK parameters will be determined for each IP: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}1.5h}$, C_{max}, T_{max}, and $T_{1/2}$. Where possible, 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 using log-linear trapezoidal interpolation. Calculations will be based on the actual sampling times recorded during the study. Concentrations below the lower limit of quantification (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 17.4 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.

All data will be listed by subject number.

17.7.4 Pharmacodynamic effects

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

The subjective parameters "craving", "satisfaction", "product-liking" and "intent to use again", measured by VAS, will be summarized for each IP using descriptive statistics during the IP use phase. Additionally, the relative and absolute change from baseline will be calculated for the subjective parameter "craving" for each IP and summarized.

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

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

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

17.7.5 Adverse events

An overview of all AEs, including SAEs, intensity, and 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.

17.8 Analysis of exploratory objectives

17.8.1 Exploratory subjective parameter

The subjective parameter "product-liking" *vs*. the subjects' usual snus/nicotine product of choice, measured through MCQ, will be summarized for each IP using descriptive statistics in a frequency table.

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

Nicotine extraction normalized PK parameters AUC_{0-inf} and C_{max} (both with and without baseline adjustment, divided by the extracted amount), will be determined for the three NP products (all 3 mg, moist and dry) and the two tobacco-based products (4 mg and 8 mg). The analysis will compare the differences in AUC_{0-inf}, C_{max}, and the extracted amount and fraction of nicotine between the NP products and the tobacco-based products.

Additionally, extraction normalized AUC_{0-inf} and C_{max} data will be presented for each IP using summary statistics.

18 REFERENCES

1. Stratton K, Shetty P, Wallace R, Bondurant S: Clearing the smoke: the science base for tobacco harm reduction--executive summary. *Tob Control*. 2001, 10:189-95. 10.1136/tc.10.2.189
2. Swedish Match Europe Division. ISRCTN44913332: A study investigating the extraction of nicotine and flavors from tobacco free nicotine pods compared to tobacco based Swedish snus. Applied November 14, 2017. Last edited August 1, 2019. Isrctn.com. https://www.isrctn.com/ISRCTN44913332 (last accessed 17OCT2024).
3. Swedish Match Europe Division. ISRCTN77807609: A study investigating the uptake to the blood circulation of nicotine from tobacco free nicotine pods compared to tobacco-based Swedish snus and American moist snuff. Applied October 3, 2018. Last edited May 28, 2020. Istctn.com. http://www.isrctn.com/ISRCTN77807609 (last accessed 17OCT2024).
4. Swedish Match Europe Division. ISRCTN14866695: A study investigating the uptake to the blood circulation and subjective effects of nicotine from tobacco free nicotine pods compared to tobacco based Swedish snus. Applied November 15, 2017. Last edited May 28, 2020. Isrctn.com. http://www.isrctn.com/ISRCTN14866695 (last accessed 17OCT2024).
5. Lunell E, Curvall M. (2011) Nicotine Delivery and Subjective Effects of Swedish Portion Snus Compared With 4 mg Nicotine Polacrilex Chewing Gum. *Nicotine & Tobacco Research* 13(7):573-578. https://doi.org/10.1093/ntr/ntr044 (last accessed 17OCT2024).
6. Swedish Match North Europe. ISRCTN30119403. A study investigating the extraction of nicotine and flavors from tobacco-free nicotine pouches. https://doi.org/10.1186/ISRCTN30119403 (last accessed 17OCT2024).
7. Swedish Match Europe Division. ISRCTN66329631. A study investigating the uptake to the blood circulation and subjective effects of nicotine from tobacco-free nicotine pouches. https://doi.org/10.1186/ISRCTN66329631 (last accessed 17OCT2024).
8. Swedish Match Europe Division. ISRCTN91637022: Effects of flavors in oral tobacco-derived nicotine pouches on nicotine exposure. https://doi.org/10.1186/ISRCTN91637022 (last accessed 17OCT2024).
9. Swedish Match Europe Division. ISRCTN13589495: Plasma nicotine concentrations following single doses of new-format nicotine pouches. https://doi.org/10.1186/ISRCTN13589495 (last accessed 17OCT2024).
10. European Commission. Clinical Trials – Regulation (EU) no. 536/2014. April 16, 2014, Published on ec.europa.eu. https://ec.europa.eu/health/human-use/clinical-trials/regulation_en (last accessed 17OCT2024).
11. National Cancer Institute Division of Cancer Treatment and Diagnosis, Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, CTCAE v5.0. November 27, 2017. Published on ctep.cancer.gov. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm (last accessed 17OCT2024).
12. World Health Organization. Blood Donor Selection: Guidelines on Assessing Donor Suitability for Blood Donation. Geneva. 2012. Chapter 4, General donor assessment. Available from https://www.ncbi.nlm.nih.gov/books/NBK138219/ (last accessed 17OCT2024).
13. European Medicines Agency. ICH E6(R2) Guideline for Good Clinical Practice. July 1, 2002. Last updated December 15, 2016. EMA/CHMP/ICH/135/1995. Published on ema.europa.eu. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice (last accessed 17OCT2024).
14. The World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. October 2024. Published on www.wma.net.

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects (last accessed 02DEC2024).

15. European Commission. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). 2016. Published on eur-lex-europa.eu. https://eur-lex.europa.eu/eli/reg/2016/679/oj (last accessed 17OCT2024).
16. European Medicines Agency. ICH E3 Structure and content of clinical study reports. July 1, 1996. CPMP/ICH/137/95. Published on ema.europa.eu. https://www.ema.europa.eu/en/ich-e3-structure-content-clinical-study-reports (last accessed 17OCT2024).
17. Kenward MG and Roger JH (2009). An improved approximation to the precision of fixed effects from restricted maximum likelihood. *Computational Statistics & Data Analysis* 53(7): 2583-2595.

19 SIGNATURES

19.1 Approval of the clinical study protocol

I, the undersigned, approve this CSP.

Sponsor signatory

[redacted]

Coordinating Investigator

[redacted]