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Effects of single doses of tobacco-based snus and 3 mg nicotine pouches on plasma nicotine levels, nicotine metabolism, and effects on the body

Submission date
14/02/2025

Recruitment status
No longer recruiting

Registration date
17/02/2025

Overall study status
Completed

Last Edited
26/02/2025

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Epidemiological data from the use of tobacco-based snus, which has been on the market for over 200 years, indicate that it has a significantly lower risk profile compared to cigarettes. However, snus contains small amounts of unwanted substances, such as tobacco-specific nitrosamines (TSNA), which can be disease-causing.
Nicotine pouches (NP) have been available on the market for about 10 years. Similar to snus, NP comes in pouches intended to be placed under the upper lip, but unlike snus, these products do not contain TSNA. The nicotine content in NP is comparable to that found in snus, which can contain up to 20 mg/pouch or more. NP can have either a dry or moist matrix, and both the format and nicotine content can vary.
When comparing the nicotine content in different oral nicotine products, it is important to consider that both the release (extraction) from the product and the absorption of nicotine in the body vary significantly depending on the product type (tobacco-based versus non-tobacco-based) and product formulation (such as pouch format, solubility, moisture content, particle size, and pH). Additionally, there is considerable interindividual variation in extraction and absorption from these products, likely due to differences in saliva production.
To evaluate the addiction potential of different nicotine contents and formats of NP in comparison with existing tobacco-based snus products, pharmacokinetic (PK) and pharmacodynamic (PD) studies are crucial.
This study will evaluate non-flavored and flavored NP and tobacco-based snus products. The aim is to identify a tobacco-based snus product for each NP product that provides comparable nicotine levels in plasma. The study will investigate how much and how quickly nicotine is absorbed and eliminated from the body, as well as how much nicotine is released from NP compared to tobacco-based snus products. Changes in pulse rate will also be measured and compared. Additionally, craving for snus, satisfaction, product-liking, and the desire to use the product again will be evaluated and compared between the study products. Overall, the study enables a thorough scientific evaluation of the properties of NP products and their safety profile.

Who can participate?
Healthy male or female volunteers aged 21 to 60 years who have used oral tobacco/NP products for 1year or over and have a minimum daily consumption of five pouches. They should be willing and able to use both tobacco-based products and NPs.

What does the study involve?
Each participant will be in the study for about 3 weeks, not including the preceding 4-week screening period. They will report to the clinic for a screening visit (Visit 1), followed by five treatment visits (Visits 2-6) on separate days.
On each treatment visit, the investigational products (IPs) will be administered as single pouches in a predetermined random order. Participants will keep the pouch still between the upper lip and gum for 30 minutes. Afterwards, each used pouch will be collected and frozen at -20°C for subsequent analysis of residual nicotine content. Blood samples for assessing nicotine levels will be collected at predefined timepoints from pre-administration to 6 hours after each administration.
The effects of the IPs will be determined using pulse rate measurements and subjective parameters at the same predefined timepoints, as well as a multiple-choice question 30 minutes after IP administration. Adverse events (AEs) will be recorded through subject interviews and will include any spontaneously reported AEs, starting from the initiation of IP administration (Visit 2) and continuing until the last treatment visit (Visit 6).

What are the possible benefits and risks of participating?
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 medical examination, which may provide them with information on their general state of health. Hence, the safety and wellbeing of the subjects are of utmost importance. Only adult participants who are well acquainted with and used to the effects of nicotine can participate in the study. 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. Notably, previous clinical studies with similar products have reported no AEs other than those likely attributed to nicotine exposure, such as salivation, nausea, and dyspepsia.

Where is the study run from?
CTC Clinical Trial Consultants AB (Sweden)

When is the study starting and how long is it expected to run for?
November 2024 to April 2025

Who is funding the study?
Swedish Match North Europe AB (Sweden)

Who is the main contact?
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Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

SM 24-03

Study information

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

Acronym
SM24-03

Study objectives
The study hypothesis is that nicotine exposure, measured as the maximum plasma concentration (Cmax), from each nicotine pouch (NP) product will be comparable to at least one of the tobacco-based snus products.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 28/01/2025, The Swedish Ethical Review Authority (Box 2110, Uppsala, SE-75002, Sweden; +46 (0)10 475 08 00; registrator@etikprovning.se), ref: 2024-08204-01

Study design
Multi-center open-label randomized cross-over single-dose administration study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Nicotine use

Interventions
Investigational products (IPs):
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

Administration and assessments:

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 thestart 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, subjects will be randomized to one of 10 use sequences using 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 thesite, 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.

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.

Intervention Type
Other

Primary outcome measure
Similarity in baseline-adjusted Cmax based on nicotine plasma concentrations after administering single doses of the three NP products and the two tobacco-based products. This is calculated based on the measurement of nicotine in plasma samples using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method at the end of the study.

Secondary outcome measures
1. Equivalence (90% confidence interval for the ratio between 0.8 and 1.25) in baseline-adjusted Cmax and area under the curve (AUC) from 0 to infinity (AUC0-inf) based on nicotine plasma concentrations after administering single doses of the three NP products and the two tobacco-based products. This is calculated based on the measurement of nicotine in plasma samples using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method at the end of the study.
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. The IP pouches will be used for 30 minutes, collected, and frozen prior to analysis using GC-MS at the end of the study. The in vivo extraction of nicotine will be calculated by subtracting the residual amount of nicotine after 30 minutes of usage of the pouches from the mean of 10 unused pouches.
3. The difference between the three NP products and the two tobacco-based products in the non-adjusted and baseline-adjusted PK parameters: AUC0inf, Cmax, time of occurrence of Cmax (Tmax), AUC from 0 to 1.5 h (AUC0-1.5h), AUC from 0 to the last measurable time point (AUC0-last), and terminal elimination half-life (T½). This is calculated based on the measurement of nicotine in plasma samples using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method at the end of the study.
4. PD (pulse rate): The difference between the three NP products and the two tobacco-based products for the highest increase from baseline (Eimax), time to the first instance of Eimax (TEimax), the Emax from time 0 to 60 min (Emax0-60), and the time to reach Emax0-60 (TEmax0-60) in pulse rate, measured using a pulse oximeter after IP administration.
5. PD parameters: The difference between the three NP products and the two tobacco-based products for the largest decrease from baseline (Edmax) and time to thefirst instance of Edmax

(TEdmax) in the subjective parameter “craving” measured using a 100 mm visual analog scale (VAS) after IP administration.
6. PD parameters: The difference between the three NP products and the two tobacco-based products for the largest value (Evmax) and time to thefirst instance of Evmax (TEvmax) in the subjective parameter “satisfaction”, measured using a 100 mm VAS after IP administration.
7. 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 administration.
8. Frequency, intensity, and seriousness of adverse events (AEs). AEs will be collected through subject interviews and will also include any AEs reported spontaneously by the subjects, starting from the initiation of IP administration (Visit2) and continuing until the last treatment visit (Visit 6).

Overall study start date
25/11/2024

Completion date
25/04/2025

Eligibility

Key inclusion 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:
5.1. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
5.2. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
5.3. Intrauterine device or intrauterine hormone-releasing system

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
21 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
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 Cmax values for all IPs.

Key exclusion criteria
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) during the last 3 months prior to screening.
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.

Date of first enrolment
05/03/2025

Date of final enrolment
25/04/2025

Locations

Countries of recruitment

Sweden

Study participating centre
CTC Clinical Trial Consultants AB (CTC)
CTC Oscar, Dag Hammarskjölds väg 10C
Uppsala
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SE-75237

Study participating centre
CTC Clinical Trial Consultants AB (CTC)
CTC GoCo, Vetenskapens gränd 11
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Sponsor information

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Sponsor type
Industry

Website
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Funder(s)

Funder type
Industry

Funder Name
Swedish Match North Europe AB

Results and Publications

Publication and dissemination plan
Planned publication in a peer reviewed journal.

Intention to publish date
31/12/2026

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 1.0	04/12/2024	17/02/2025	No	No