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Comparing nicotine exposure from nicotine pouches and tobacco-based snus: a three-part study.

Submission date
26/03/2025

Recruitment status
Recruiting

Registration date
27/03/2025

Overall study status
Ongoing

Last Edited
13/06/2025

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
The use of oral smokeless tobacco products (STPs), such as Swedish snus and moist snuff, is not associated with exposure to the numerous combustion compounds found in tobacco smoke, many of which can cause cancer and inflammation in the body. It also avoids chronic irritation in the upper and lower airways resulting from the inhalation of tobacco smoke. Therefore, it is generally accepted that the health risks associated with oral STPs are substantially lower than those of cigarette smoking.
Swedish snus, a long-standing product on the market, typically contains 8-10 mg of nicotine per pouch, with some varieties offering both lower and higher nicotine contents. Numerous research studies have delved into the extent of nicotine exposure and the long-term health risks associated with daily use of tobacco-based snus.
Nicotine pouch (NP) products, which have been available for a few years, share some similarities with certain oral STPs as they are designed to be placed under the upper lip. However, unlike STPs, NPs do not contain tobacco leaves or certain harmful substances found in STPs, such as tobacco-specific nitrosamines. As a relatively new product on the market, the long-term health effects of NPs are not yet known. Most NP products on the Swedish market contain between 1.5 and 17 mg of nicotine per pouch. However, in extreme cases, certain NPs can contain up to 150 mg of nicotine per pouch, posing serious health risks, especially for new users or those with low nicotine tolerance.
The nicotine content is not synonymous with nicotine exposure. The extraction and uptake of nicotine can vary substantially depending on the product type and formulation, and there is substantial variation observed between individuals. Moreover, the pattern of use, including the duration of usage and the number of pouches/portions used per day, also influences nicotine exposure. To examine the impact of nicotine content in NPs on nicotine exposure, it is essential to assess both addiction potential through pharmacokinetic and pharmacodynamic (PK/PD) studies and evaluate real-life nicotine exposure using biomarkers of exposure (BoE).
This study aims to gain a comprehensive understanding of how nicotine content affects actual exposure, addiction potential, and whether the long-term health risks of NPs can be estimated based on the epidemiological studies available for tobacco-based snus. The study is organized into three parts:

Part 1: Baseline assessment – This involves using the subject´s preferred brand of Swedish snus product. The focus is on measuring product usage, exposure to nicotine and tobacco-specific nitrosamines, and the levels of these compounds in the urine.
Part 2: Evaluating addition potential – This part will compare the nicotine delivery and uptake of three moist NP products with different nicotine content (6, 11 and 16.6 mg) to a Swedish snus product with 18 mg of nicotine and the subject´s own brand snus product. Additionally, subjective parameters, such as user satisfaction and product liking, will be assessed.
Part 3: Exploring self-titration behaviors – This part aims to assess self-titration behaviors by having the subject replace their own brand snus product with one of the NP products tested in Part 2 for a period of 14 days. The focus will be on measuring product usage, exposure to nicotine and tobacco-specific nitrosamines, and the levels of these compounds in the urine. The aim also includes comparing these parameters with those assessed in Part 1. This approach will provide a comprehensive understanding of self-titration behaviors in a real-world context.

Who can participate?
Healthy volunteers aged 19 to 60 years who have used Swedish snus products for 1 year or over, with a minimum daily consumption of five pouches/portions, who are willing and able to use both Swedish snus and NPs with high nicotine content, while abstaining from other tobacco /nicotine products during the study, may be considered to be eligible for participation in the study.

What does the study involve?
The study consists of three parts, and each volunteer will participate in the study for a period of about 7 weeks, not including the preceding screening period. Participants will report to the study site for a screening visit (Visit 1) followed by:
Part 1 (Visit 2-3): This part will involve the use of the participant's own brand of snus product for 14 days, with visits to the clinic before and after this period. Participants will document their product use, collect used pouches/portions, and provide urine samples during a 24-hour in-clinic visit for the assessment of biomarkers of exposure.
Part 2 (Visit 4-8): This part involves a single IP use for 30 minutes during each of the five study visits. The IPs include: three nicotine pouch (NP) products (6, 11 and 16.6 mg), one Swedish snus product (18 mg), and the participant´s own brand snus product. The IPs will be used for 30 minutes, and blood samples will be collected up to 6 hours after each IP administration. The pulse rate will be measured, and subjective parameters will be assessed. Adverse events (AEs) will be recorded from the initiation of IP administration (Visit 2) and continue until the last treatment visit.
Part 3 (Visit 9-10): This part will involve the complete substitution of the participant´s own brand snus product with an NP product (chosen from the three NP products tested in Part 2) for 14 days, with visits to the clinic before and after this period. Participants will document their product use, collect used pouches, and provide urine samples during a 24-hour in-clinic visit for the assessment of biomarkers of exposure.

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 brief 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?
Clinical Trial Consultants AB (Sweden)

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

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

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
SM 24-01

Study information

Scientific Title
Examining the effects of nicotine content in nicotine pouches on nicotine exposure under controlled settings and during ad libitum use: a comprehensive three-part study

Acronym
SM24-01

Study objectives
The study hypothesis is that the nicotine exposure from three nicotine pouches (NPs) with different amounts of nicotine is not substantially higher than the nicotine exposure from tobacco-based snus.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/11/2024, The Swedish Ethical Review Authority (Box 2110, Uppsala, SE-75002, Sweden; +46 (0)10 475 08 00; registrator@etikprovning.se), ref: 2024-06619-01

Study design
Multi-center open-label three-part study: observational non-randomized (Part 1), randomized cross-over (Part 2), and interventional non-randomized (Part 3)

Primary study design
Interventional

Secondary study design
Observational non-randomized (Part 1), randomized cross-over (Part 2), and interventional non-randomized (Part 3)

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
The screening visit (Visit 1) will take place within 5 weeks prior to start of Part 2 (Visit 4) 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. During the screening visit, subjects will complete a nicotine dependence questionnaire. They will also select the Swedish snus product, either a pouch or loose snus, which they will use exclusively during Part 1 of the study. Subjects will purchase this product themselves. The chosen product should be the brand they predominantly used in the past month, unless they did not exclusively use a single brand. This selection will determine the nicotine strength and flavor variation, as these factors vary within the same brand. For Part 2 of the study and for chemical analyses, the Sponsor will purchase the selected snus product.

Part 1: Ad libitum use of own brand snus

At Visit 2 (first day of Part 1), eligible subjects will return to the study site to receive collection materials for used pouches, undergo eDiary training, and undergo interviews regarding their health status and medications used.

After Visit 2, subjects will exclusively use their product of choice ad libitum, following their regular pattern of use. They will document their consumption via an eDiary (ViedocMe) during a 14-day study period, recording the number of pouches/portions used per day, the estimated usage time per pouch/portion, and whether they opened a new snus can for pouch/portion usage once per day. Also, subjects will collect 4 used pouches/portions on two separate days in the first week (Samples A) and on two separate days in the second week (Samples B) and store these in a freezer (≤ -18°C). In total, eight pouches/portions will be collected per week. Subjects will receive instructions on how to collect used pouches/loose snus and will be provided with collection containers for storing them and a cooling bag for transportation of the used pouches to the study site.

At Visit 3 (14 days [allowed time window: +3 days] after Visit 2), the subjects will return to the study site in the morning. They will bring the collected frozen pouches/portions for extraction analysis. During this visit, subjects will undergo interviews regarding their health status and medications used, the specific Swedish snus product they used (including its strength and

flavor), and their compliance with the eDiary will be assessed. Additionally, a 24-hour urine collection (allowed time window: ±15minutes) will begin in the morning. The subject will remain on-site until the following morning, using the snus product ad libitum. Urine will be continuously collected during this period for the analysis of biomarkers of exposure (BoE).

Part 2: Single IP use in a five-way cross-over

At Visit 4, the subjects will return to the study site for the first IP use visit of Part 2.Subjects shall abstain from tobacco/nicotine products as well as smoking (cigarettes or e-cigarettes) for 12 hours prior to each IP use visit (Visits 4 to 8). 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/portions in a pre-determined randomized order. Randomization will take place before the first IP use of Part 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 - 6 mg
B = NP 2 - 11 mg
C = NP 3 – 16.6 mg
D = Own brand snus product
E = Swedish pouch snus - 18 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 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.

During Visits 4 to 8, subjects will keep the pouch/portion between their lip and gum for 30 minutes and will be instructed not to eat, drink, chew gum, or brush their teeth for 30 minutes before, during, and 30 minutes after the IP use.

After 30 minutes, each used pouch/portion will be collected and frozen (-20°C) pending analysis of residual nicotine content. Unused pouches/portions 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 hours after each IP use. The PD effects of the IPs will be determined using pulse rate measurements and subjective parameters (using visual analogue scale [VAS] questions) at the same pre-defined time points, as well as an MCQ 30 minutes 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 4), and continuing until the last IP use visit (Visit 8).

Visits 5 to 8 will follow the same schedule as Visit 4. Each visit will be scheduled on separate days, preferably with at least 24 hours between visits. However, it is acceptable to have visits on consecutive days, as long as all 5 visits are not scheduled consecutively.

At the end of Visit 8, the subject will receive one can of each of the three moist NP products with varying strengths (6 mg, 11 mg, and 16.6 mg) used in Part 2. Importantly, the subjects will be blinded to the nicotine strength of these three products. The subject will test these at home over 23days to ensure they find a suitable replacement for their own brand snus product to be used in Part 3.

Part 3: Ad libitum use of nicotine pouch product

At Visit 9 (first day of Part 3), the subjects will return to the study site, and then the chosen NP product (6 mg/unit, 11 mg/unit or 16.6 mg/unit) will be documented. Based on the subject's reported consumption, they will be provided with the NP product to be exclusively used ad libitum for 14days (allowed time window: +3 days). During this visit, subjects will undergo interviews regarding any experienced AEs. Subjects will be reminded of how to document their consumption using the eDiary and how to collect used pouches. The subjects will also be provided with collection containers for storing the used pouches and a cooling bag for transportation of the used pouches to the study site.

From the day after Visit 9, subjects will completely switch from their own brand snus product to the chosen moist NP product for 14 days, using it ad libitum. Subjects will document their consumption once per day via an eDiary throughout the 14-day study period (recording the number of pouches used per day, the estimated usage time per pouch, and whether they opened a new can). Additionally, subjects will collect four used pouches on two separate days during the first week (Samples A) and on two separate days during the second week (Samples B), storing them in a freezer (≤ -18°C). In total, eight pouches will be collected per week.

At Visit 10 (14 days after Visit 9), the subjects will return to the study site in the morning. They will bring the collected frozen pouches for extraction analysis. During this visit, subjects will undergo interviews regarding any experienced AEs, the NP product used, and their compliance with the eDiary will be assessed. Additionally, a 24-hour urine collection (allowed time window: ±15minutes) will begin in the morning. Subject will remain on-site until the following morning, using the selected NP product ad libitum. The urine will be continuously collected during this period for the analysis of BoE.

The subject may leave the study site after completion of the 24-hour urine collection and final assessment of AEs and concomitant medications. This is the end of the subject's study participation.

Intervention Type

Other

Primary outcome measure

Nicotine exposure, as measured by baseline-adjusted area under the plasma concentration vs time curve from 0 to infinity (AUC0-inf) based on nicotine plasma concentrations, compared between the moist NP 11 mg product and the comparator product, Swedish snus 18 mg. (The goal is to demonstrate that the upper bound of the 95 % confidence interval for the ratio for nicotine exposure between the moist NP 11 mg product and the comparator product is at or below 1.25). 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. The difference in in vivo extracted amount (mg/unit) and extracted fraction (%) of nicotine between the moist NP 6 mg, 11 mg, and 16.6 mg products and the comparator products, Swedish snus 18 mg and own brand snus product. The IP pouches will be used for 30 min, collected, and frozen prior to analysis using gas chromatography - mass spectrometry (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 min of usage of the pouches from the mean of 10 unused pouches.
2.1. The difference between the moist NP 6 mg, 11 mg, and 16.6 mg products and the comparator products, Swedish snus 18 mg and own brand snus product, in the non-adjusted and baseline-adjusted PK parameters based on plasma concentrations of nicotine:
2.1.1. AUC0-inf
2.1.2. Maximum observed plasma concentration (Cmax)
2.1.3. Time to Cmax (Tmax)
2.1.4. AUC from 0 to 1.5 hours (AUC0-1.5h)
2.1.5. AUC from 0 to time of last measurable time point (AUC0-last)
2.1.6. Terminal elimination half-life (T1/2)
This is calculated based on the measurement of nicotine in plasma samples using a validated LC-MS/MS analytical method at the end of the study.
2.2. Nicotine exposure, as measured by non-adjusted and baseline-adjusted AUC0-inf, compared between the moist NP 6 mg and NP 16.6 mg products and the comparator products, Swedish snus 18 mg, and the own brand snus product. This comparison also includes the NP 11 mg product and the own brand snus product. (The goal is to demonstrate that the upper bound of the 95% confidence interval for the ratio for nicotine exposure between the moist NP products and the comparator products is at or below 1.25). This is calculated based on the measurement of nicotine in plasma samples using a validated LC-MS/MS analytical method at the end of the study.
3.1. The difference between the moist NP 6 mg, 11 mg, and 16.6 mg products and the comparator products, Swedish snus 18 mg and own brand snus product, for the highest recorded increase (Emax), the time to Emax (TEmax), the Emax from time 0 to 60 minutes (Emax0-60), and the time to reach Emax0-60 (TEmax0-60) in pulse rate from baseline, measured using a pulse oximeter after IP use.
3.2. The difference between the moist NP 6 mg, 11 mg, and 16.6 mg products and the comparator products, Swedish snus 18 mg and own brand snus product, for the largest recorded decrease (Emax) in the subjective parameter “craving” and the highest recorded value for “satisfaction”, measured using a 100 mm visual analogue scale (VAS) after IP use.
3.3. The difference between the moist NP 6 mg, 11 mg, and 16.6 mg products and the comparator products, Swedish snus 18 mg and own brand snus product, for the subjective parameters “product-liking” and “intent to use again”, measured using a 100 mm VAS 30 min

after IP use.
4. 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 use (Visit 4), and continuing until the last IP use visit (Visit 10).

Overall study start date
22/05/2024

Completion date
02/10/2025

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 products for ≥1 year, with a minimum daily consumption of 5 pouches/portions, who are willing and able to use both Swedish pouch snus and NPs with high nicotine content while abstaining from other tobacco/nicotine products during the study. (Dual use of Swedish snus and NPs before inclusion will be permitted, but subjects should exclusively use their usual brand of a Swedish snus product (including strength and flavor) ad libitum during Part 1).
3. Healthy male or female subject aged 19 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 child-bearing potential must practice abstinence from heterosexual intercourse (only allowed when this is the preferred and usual lifestyle of the subject) or must 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
19 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
The study will include approximately 53 tobacco-based snus users with the aim of randomizing at least 53 subjects in Part 2 and achieving 45 evaluable subjects (for Part 2). Efforts will be made to include at least 21 female subjects (approximately 40%). However, a minimum of 11 female subjects (approximately 20%) will be considered acceptable. Additionally, efforts will be made to include 10 to 15 regular users of loose snus. These users will use a loose snus of their choice as their own brand product during Part 1 and Part 2. Each subject will participate in the study for a period of approximately 7 weeks, not including the preceding 5-week screening period.

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 who are 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 screening 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
07/04/2025

Date of final enrolment
02/10/2025

Locations

Countries of recruitment
Sweden

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
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Results and Publications

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

Intention to publish date
30/11/2026

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 2.0	09/10/2024	26/03/2025	No	No