ISRCTN13589495 https://doi.org/10.1186/ISRCTN13589495

Plasma nicotine concentrations following single doses of new-format nicotine pouches

Submission date
04/12/2023

Recruitment status
No longer recruiting

Registration date
05/12/2023

Overall study status
Completed

Last Edited
03/09/2025

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Use of oral smokeless tobacco products (STPs), such as Swedish snus and moist snuff, is by definition unassociated with exposure to the many thousands of combustion compounds found in tobacco smoke (many of which can cause cancer and inflammation in the body), 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 STPs has substantially lower health risks than cigarette smoking. However, oral STPs are still debated because they contain tobacco and can be addictive. The tobacco in oral STPs contains measurable amounts of potentially harmful substances, but these levels are very low.
Nicotine pouch (NP) products have been on the market for a few years. NPs share some similarities with certain oral STPs; they come in pouches intended to be placed under the upper lip and do not require spitting. Unlike STPs, NPs do not have tobacco leaves and do not contain certain harmful substances found in STPs, like nitrosamines or polycyclic hydrocarbons. The nicotine content in the NPs studied here is 3 mg and 6 mg, which is comparable to the nicotine levels in STPs available in Scandinavia and the United States (ranging from 3 mg/unit to over 20 mg/unit). However, when comparing the nicotine content of different nicotine delivery products, it is vital to consider that nicotine extraction and uptake can vary considerably depending on the product type (tobacco-based or non-tobacco-based) and the product's formulation (including factors like pouch size, solubility, water content, particle size, pH, etc). Moreover, there is a significant range of variation in how individuals absorb orally consumed STPs, likely due to differences in saliva production, leading to a wide range of nicotine extraction and uptake level.
While many NP products are available, only a few have been scientifically evaluated so far. It has been suggested that certain flavors may enhance nicotine uptake, but this has not been thoroughly examined in this product category.
This study will examine a new format of NP products (both flavored and unflavored). While the general aspects of nicotine metabolism are known, there is a need to comprehend how the new NP format delivers and is absorbed in the body. This study will investigate the nicotine delivery and uptake of the new format NP, including two unflavored products (3 mg and 6 mg) and eight flavored products (6 mg), in comparison with Longhorn Pouch Natural 18 mg. The study will also assess the physiological effects of these products.

Who can participate?
Healthy male or female tobacco-based snus users aged 21 to 60 years who have used oral tobacco/nicotine pouch products for 1 year or more, with a minimum daily consumption of five or more pouches, who are willing and able to use both tobacco-based moist snuff and NPs with high nicotine content, may be considered to be eligible for participation in the study.

What does the study involve?
Participants will report to the study site for a screening visit (Visit 1) followed by 11 treatment visits (Visits 2-12) on separate days. The screening will take place within 4 weeks before Visit 2. The investigational products (IPs) in this study include 10 NP products and one moist-snuff product (comparator). 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 will be recorded from the initiation of IP administration (Visit 2) and continue until the last treatment visit (Visit 12). Each participant will participate in the study for a period of around 5 weeks, not including the preceding screening period.

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 participants, 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 participants are of utmost importance. Similar products are currently commercially available and only adult participants who are well acquainted with and used to the effects of nicotine can participate in the study. So far, no adverse events have been reported in previous studies with similar products, apart from effects likely to be related to nicotine exposure (such as salivation, nausea, headache, and indigestion).

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?
September 2023 to February 2024

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

Who is the main contact?
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Contact information

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Public, Scientific

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Additional identifiers

Protocol serial number
SM23-01

Study information

Scientific Title
Nicotine plasma concentrations, pharmacokinetics, and pharmacodynamics following single doses of nicotine pouches with a new format in current, daily oral tobacco/nicotine pouch users

Acronym
SM23-01

Study objectives
The study hypothesis is that the new format unflavored nicotine pouch (NP) 6 mg product does not result in substantially higher nicotine exposure compared to the comparator product, Longhorn Natural 18 mg.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/12/2023, Swedish Ethical Review Authority (Box 2110, Uppsala, SE-750 02, Sweden; +46 (0)104750800; registrator@etikprovning.se), ref: 2023-06053-01

Primary study design
Interventional

Study design
Multi-center open-label randomized 11-way cross-over single-dose administration study

Study type(s)
Other

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

Interventions
Participants will report to the study site for a screening visit (Visit 1) followed by 11 treatment visits (Visits 2-12) on separate days. The screening will take place within 4 weeks before Visit 2. At Visit 2, participants will be randomized to one of 11 administration sequences. As this is an open-label study, the IP administration 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, day, 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.

Investigational products (IPs):
NP 1 - Unflavored - 3 mg
NP 2 - Unflavored - 6 mg
NP 3 - Flavor A - 6 mg
NP 4 - Flavor B - 6 mg
NP 5 - Flavor C - 6 mg
NP 6 - Flavor D - 6 mg
NP 7 - Flavor E - 6 mg
NP 8 - Flavor F - 6 mg
NP 9 - Flavor G - 6 mg
NP 10 - Flavor H - 6 mg
Longhorn Natural (comparator) - 18 mg

The IPs will be administered as single pouches in a predetermined randomized order and used for 30 minutes. After 30 minutes, each used pouch will be collected and frozen at -20°C pending analysis of residual nicotine content. Blood samples for the assessment of nicotine plasma concentrations and pharmacokinetic (PK) parameters will be collected at pre-defined time points, from pre-administration to 6 hours after each IP administration. The pharmacodynamic (PD) effects of the IPs will be determined using pulse rate measurements and subjective parameters, assessed using a 100 mm visual analogue scale, at the same pre-defined time points, as well as through a multiple-choice question (MCQ) 30 minutes after IP administration. Adverse events (AEs) will be recorded through subject interviews and will also include any AEs reported spontaneously by the subjects. This data collection will start from the initiation of IP administration (Visit 2) and continue until the last treatment visit (Visit 12).

Intervention Type
Other

Primary outcome(s)

Nicotine exposure measured by baseline-adjusted area under the plasma concentration vs time curve from 0 to infinity (AUC0-inf) based on nicotine plasma concentrations. Blood samples will be collected at predefined timepoints: -10 min before IP administration, and at 5, 10, 15, 20, 30, 40, 60, 90, 120, 240, and 360 minutes post-IP administration. The goal is to demonstrate that the upper bound of the 90% confidence interval of the ratio for nicotine exposure of the new format unflavored NP 6 mg product and the comparator product is 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.

Key secondary outcome(s)

1. Extraction from pouches: The difference in in vivo extracted amount (mg/unit) and extracted fraction (%) of nicotine between the unflavored NP 3 mg and 6 mg products and the comparator product, Longhorn Natural 18 mg. The IP pouches will be used for 30 minutes, 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 minutes of usage of the pouches from the mean of 10 unused pouches.
2. PK of nicotine in plasma: The difference between the unflavored NP 3 mg and 6 mg products and the comparator product, Longhorn Natural 18 mg, in the non-adjusted and baseline-adjusted PK parameters based on plasma concentrations of nicotine:
2.1. AUC0-inf
2.2. Maximum observed concentration (Cmax)
2.3. Time of occurrence of Cmax (Tmax)
2.4. AUC from 0 to 1.5 hours (AUC0-1.5h)
2.5. AUC from 0 to time of last measurable time point (AUC0-last)
2.6. Terminal elimination half-life (T1/2)
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.
3.1. PD (pulse rate): The difference between the unflavored NP 3 mg and 6 mg products and the comparator product, Longhorn Natural 18 mg, for the highest recorded increase (Emax) in pulse rate from baseline, measured using a pulse oximeter after IP administration.
3.2. PD parameters: The difference between the unflavored NP 3 mg and 6 mg products and the comparator product, Longhorn Natural 18 mg, for the highest recorded value (Emax) in the subjective parameters “craving” and “satisfaction”, measured using a 100 mm visual analogue scale (VAS) after IP administration.
3.3. PD (subjective outcome parameters): The difference between the unflavored NP 3 mg and 6 mg products and the comparator product, Longhorn Natural 18 mg, for the subjective parameters “product-liking” and “intent to use again”, measured using a 100 mm VAS 30 minutes after IP administration.
4. Extraction from pouches: The difference in in vivo extracted amount (mg/unit) and extracted fraction (%) of nicotine between the unflavored NP 6 mg and the flavored NP 6 mg 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.
5.1. PK of nicotine in plasma: The equivalence between the unflavored NP 6 mg and flavored NP 6 mg products in the non-adjusted and baseline-adjusted PK parameters AUC0-inf and Cmax based on plasma concentrations of nicotine.
5.2. PK of nicotine in plasma: The difference between the unflavored NP 6 mg and flavored NP 6

mg products in the non-adjusted and baseline-adjusted PK parameters Tmax, AUC0-1.5h, and AUC0-last and T1/2. 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.
6.1. PD (pulse rate): The difference between the unflavored NP 6 mg and flavored NP 6 mg products for the highest recorded increase (Emax) in pulse rate from baseline, measured using a pulse oximeter after IP administration.
6.2. PD parameters: The difference between the unflavored NP 6 mg and flavored NP 6 mg products for the highest recorded value (Emax) in the subjective parameters “craving” and “satisfaction”, measured using a 100 mm VAS after IP administration.
6.3. PD (subjective outcome parameters): The difference between the unflavored NP 6 mg and flavored NP 6 mg products for the subjective parameters “product-liking” and “intent to use again”, measured using a 100 mm VAS 30 min after IP administration.
7. 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 (Visit 2) and continuing until the last treatment visit (Visit 12).

Completion date
23/02/2024

Eligibility

Key inclusion criteria
1. Willing and able to give written informed consent for participation in the study
2. Subjects who have used oral tobacco/nicotine products for ≥1 year, with a minimum daily consumption of five or more pouches who are willing and able to use both tobacco-based moist snuff and NPs with high nicotine content
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. Successful completion of the product familiarization session for the comparator product use is required before the first IP administration. The subject should be able to follow the instructions, tolerate the product, and not experience any adverse effects different from what is expected during typical smokeless pouch use in the training session.
6. Female subjects of childbearing 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:
6.1. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
6.2. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
6.3. Intrauterine device or intrauterine hormone-releasing system

Participant type(s)
Healthy volunteer

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
21 Years

Upper age limit
60 Years

Sex
All

Total final enrolment
38

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 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 administration. 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), 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

12/12/2023

Date of final enrolment
23/12/2023

Locations

Countries of recruitment
Sweden

Study participating centre
Clinical Trial Consultants AB (CTC) Oscar
Dag Hammarskjölds väg 10C
Uppsala
Sweden
SE-752 37

Study participating centre
CTC Karolinska
Karolinska vägen 22
Solna
Sweden
SE-171 64

Study participating centre
CTC Ebbepark
Ebbegatan 3
Linköping
Sweden
SE-582 16

Sponsor information

Organisation
Swedish Match North Europe AB

Funder(s)

Funder type

Industry

Funder Name
Swedish Match North Europe AB

Results and Publications

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	29/09/2023	24/02/2025	No	No