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A study investigating the uptake to the blood circulation and subjective effects of nicotine from tobacco-free nicotine pouches

Submission date
08/02/2021

Recruitment status
No longer recruiting

Registration date
09/02/2021

Overall study status
Completed

Last Edited
12/12/2023

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
Sweden has the lowest prevalence of smoking in Europe, particularly among males. It is widely accepted that one contributory factor to this trend is that snus has replaced cigarettes as the tobacco product of choice among many male and some female smokers.
Nicotine is the substance that is thought to contribute the most to the dependency of using any type of tobacco product, and nicotine exposure may contribute to adverse pregnancy outcomes. In addition, oral tobacco products typically contain low levels of unwanted substances (including nitrosamines and polycyclic hydrocarbons) that have been classified as human carcinogens. So, although the health effects are substantially smaller for oral tobacco compared to cigarette smoking, some adverse effects cannot be ruled out, in particular not effects related to the nicotine exposure.
Traditionally there has been no non-tobacco-based nicotine product intended for recreational use. Despite the vast risk differential between snus and cigarettes in terms of adverse long-term health effects, snus remains a controversial product as it contains tobacco, is intended for recreational use, and causes dependency. The tobacco component of snus explains why it contains measurable amounts of unwanted, potentially carcinogenic constituents, albeit at very low concentrations. Non-tobacco-based nicotine products (e.g. ZYN) have been commercially available for a few years. They have some features that are similar to snus since they come in pouches that are intended to be placed under the upper lip. However, in contrast to snus, these products contain no nitrosamines or polycyclic hydrocarbons, which are the two main classes of unwanted substances in snus. The nicotine content in ZYN is comparable to that in snus and many other oral tobacco products that are currently common on the market in Scandinavia and the US.
It has been suggested that some flavors could enhance nicotine uptake, which has not previously been fully scientifically investigated for this product category. Similarly, there is a lack of scientific data regarding any possible impact of flavoring on the pharmacodynamics.
This study is a part of the effort by Swedish Match to assess if flavors affect the nicotine uptake, pharmacokinetics (what the body does to a drug) and pharmacodynamics (what a drug does to the body) of ZYN ULTRA products, which have a different formulation compared to previously developed ZYN products. While the general pharmacokinetic characteristics of nicotine are

known, the nicotine delivery, uptake and subsequent exposure associated with use of ZYN ULTRA are not. The overarching aim of the study is to ensure that the flavored ZYN ULTRA products do not entail a higher nicotine exposure than the equivalent unflavored ZYN ULTRA product.

Who can participate?
Healthy male or female volunteers aged 19 or older who have used tobacco-based snus for over 1 year

What does the study involve?
The participants will come for nine treatment visits to the clinic, in addition to a visit for screening and a follow-up telephone visit. On the nine different treatment days participants will use one of nine different products, including the comparator product. The treatments are all administered as single doses in a pre-determined random order. The participant keeps the pouch still between the upper lip and the gum for 60 minutes. Blood levels of nicotine are followed over 6 hours after administration.

What are the possible benefits and risks of participating?
There are no possible benefits to participating. The tested products are commercially available and only participants who are well acquainted with and used to the effects of nicotine can participate. The only side effects are the effects likely to be related to nicotine exposure (such as salivation, nausea, and dyspepsia [indigestion]).

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?
October 2020 to August 2021 (updated 01/04/2021, previously: May 2021)

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

Who is the main contact?
Dr Camilla Pramfalk
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(updated 08/04/2021, previously: Dr Sara Moses
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
SM 20-02

Study information

Scientific Title
Nicotine plasma concentrations, pharmacokinetics and pharmacodynamics of single doses of flavored non-tobacco-based nicotine pouches (ZYN ULTRA) in current, daily snus users

Acronym
20-02

Study objectives
The primary objective of the study is to evaluate the impact of flavor on nicotine exposure, after the administration of single doses of ZYN ULTRA Smooth (unflavored) and ZYN ULTRA Wintergreen (flavored).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/01/2021, Swedish Ethical Review Authority (Box 2110, 750 02 Uppsala, Sweden; +46 (1)104750800; registrator@etikprovning.se), ref: Dnr 2020-06740

Study design
Single-centre open randomized nine-way cross-over single-dose administration study

Primary study design
Interventional

Study type(s)
Other

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

Interventions
Investigational Product (IP), dosage and mode of administration

1. ZYN ULTRA Wintergreen containing 9 mg nicotine per portion (1 pouch)
2. ZYN ULTRA Cool Mint containing 9 mg nicotine per portion (1 pouch)
3. ZYN ULTRA Spearmint containing 9 mg nicotine per portion (1 pouch)
4. ZYN ULTRA Peppermint containing 9 mg nicotine per portion (1 pouch)
5. ZYN ULTRA Citrus containing 9 mg nicotine per portion (1 pouch)
6. ZYN ULTRA Chill containing 9 mg nicotine per portion (1 pouch)
7. ZYN ULTRA Menthol containing 9 mg nicotine per portion (1 pouch)
8. ZYN ULTRA Deep Freeze containing 9 mg nicotine per portion (1 pouch)

Comparator product:
ZYN ULTRA Smooth containing 9 mg nicotine per portion (1 pouch)

The participants will come for nine treatment visits to the clinic, in addition to a visit for screening and a follow-up (FU) telephone visit.
On the nine different treatment days participants will use one of nine different products of IP or reference, respectively. The treatments are all administered as single doses in a pre-determined random order. The participant keeps the pouch still between the upper lip and the gum for 60 minutes. Blood levels of nicotine, pulse rate and subjective effects are followed over 6 hours after administration.

Intervention Type
Other

Primary outcome(s)
Pharmacokinetics of nicotine in plasma: the equivalence (90% confidence interval between 0.8 and 1.25) in AUCinf based on nicotine plasma concentrations from 0 to 6 h after the administration of single doses of ZYN ULTRA Smooth (unflavored) and ZYN ULTRA Wintergreen (flavored), calculated based on measurement of nicotine in blood samples with a liquid chromatography-mass spectrometry (LC-MS/MS) analytical method at the completion of the study.

Key secondary outcome(s))
1. The difference in the highest recorded increase in pulse rate from baseline, measured using a pulse oximeter at pre-set time points up to 6 hours after IP administration (-10 min pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h:15 min, 1 h:30 min,
2 h, 4 h, 6 h post-dose), between the unflavored ZYN ULTRA Smooth and the flavored ZYN ULTRA products
2. The difference in subjective parameters, measured using a 100 mm visual analogue scale (VAS) at pre-set time points up to 6 hours after IP administration (-10 min pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h:15 min, 1 h:30 min, 2 h, 4 h, 6 h post-dose), between the unflavored ZYN ULTRA Smooth and the flavored ZYN ULTRA products
3. Pharmacokinetics of nicotine in plasma: the equivalence in Cmax and AUCinf based on nicotine plasma concentrations after the administration of single doses of ZYN ULTRA Smooth (unflavored) and the flavored ZYN ULTRA products, calculated based on measurement of nicotine in blood samples with a liquid chromatography-mass spectrometry (LC-MS/MS) analytical method at the completion of the study. Blood samples for analysis of PK parameters will be collected -10 min pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h:15 min, 1 h:30 min, 2 h, 4 h, 6 h post-dose
4. Pharmacokinetics of nicotine in plasma: the calculated difference in Tmax, AUC0-1.5h, AUC0-t, and T1/2 between the unflavored ZYN ULTRA Smooth and the flavored ZYN ULTRA products

based on nicotine plasma concentrations, measured using liquid chromatography-mass spectrometry (LC-MS/MS) analytical method at the completion of the study, from samples collected -10 min pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h:15 min, 1 h:30 min, 2 h, 4 h, 6 h post-dose
5. The difference in in vivo extracted amount of nicotine (mg/unit) and extracted fraction (%) of nicotine between the unflavored ZYN ULTRA Smooth and the flavored ZYN ULTRA products analysed at t=60 min (removal of pouch) using GC-MS analysis and calculated by subtracting the residual amount after use from the mean of 10 unused pouches. Used pouches are frozen after dosing and analysis using GC-MS is performed at the end of the trial
6. The correlation between the total extracted amount of nicotine, Cmax and AUCinf measured as statistical analysis calculations at the completion of the study

Completion date
31/08/2021

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, preferably brands with nicotine content ≥1%, and is willing and able to use brands with nicotine content ≥1%
3. Healthy male or female subject aged ≥19 years
4. Clinically normal medical history, physical findings, vital signs, ECG, and laboratory values at the time of screening, as judged by the investigator
5. WOCBP must be willing to use a sufficient contraceptive method for the duration of the study, this includes mechanical barrier (e.g., a male condom or a female diaphragm), combined [estrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal anticonception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device (IUD) or intrauterine system (IUS). Sexual abstinence is allowed when this is the preferred and usual lifestyle of the subject

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
44

Key exclusion criteria

1. A history or presence of diagnosed hypertension or any cardiovascular disease.
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 investigational product 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. Subjects who are pregnant, breastfeeding, or intend to become pregnant during the course of the study.
4. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV).
5. A history of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity to similar flavoring agents as those found in the IPs (e.g. spearmint in toothpaste) as judged by the investigator.
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6. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to first administration of the IP. Positive results that are expected given the subject's medical history and prescribed medications can be disregarded as judged by the investigator.
7. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the investigator.
8. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during the three months prior to screening.
9. Subjects who intend to change their nicotine consumption habit, including the intention to stop using nicotine products, within the next three months from the screening visit, as judged by the investigator.
10. The investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.

Date of first enrolment
11/02/2021

Date of final enrolment
23/03/2021

Locations

Countries of recruitment
Sweden

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

Sponsor information

Organisation
Swedish Match

Funder(s)

Funder type
Industry

Funder Name
Swedish Match North Europe

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?
Participant information sheet	Participant information sheet version 1.0	11/11/2025	11/11/2025	No	Yes
Protocol file		07/12/2020	30/11/2022	No	No