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A study investigating the uptake to the blood circulation of nicotine from tobacco-free nicotine pouches compared to American moist snuff pouches

Submission date
23/01/2020

Recruitment status
No longer recruiting

Registration date
28/07/2020

Overall study status
Completed

Last Edited
11/03/2025

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
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.
Snus is a moist form of smokeless tobacco, which is usually placed under the upper lip. Oral tobacco, like snus and moist snuff, is capable of rapidly delivering nicotine to the bloodstream. It may therefore be more satisfactory to smokers than currently available pharmaceutical nicotine replacement therapies (NRT). The use of smokeless tobacco is unassociated with exposure to the many thousands of combustion products found in tobacco smoke. Therefore, it is generally accepted that use of smokeless tobacco products has substantially lower health risks than cigarette smoking, although some adverse effects cannot be ruled out, in particular not effects related to the nicotine exposure. Despite the big difference 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 is potentially addictive. Recently, a novel, non-tobacco-based nicotine product (ZYN®) has been developed and is now commercially available both in Europe and in the U.S. It has some features similar to snus, but ZYN does not contain the typical unwanted substances common in tobacco-based snus and moist snuff and thus represents an improvement for the protection of public health. In previous studies, Swedish Match has investigated the nicotine delivery and uptake for ZYN compared to snus and moist snuff, in the current study two new versions of ZYN pouches (ZYN moist and ZYN DRY mini) with different nicotine content will be compared to moist snuff.
The nicotine delivery profile of a product determines its effectiveness to function as an alternative to cigarettes and snus. When comparing the nicotine content of different nicotine-delivery products it is important to consider that the nicotine uptake varies considerably depending on product type, product formulation and use. In view of these circumstances, it is justified to study the nicotine delivery and uptake profile of the new ZYN products in comparison with commercially available moist snuff on the U.S. markets. These brands typically have a higher nicotine content and/or larger pouch size. The overall aim of the study is to ensure

that the ZYN products do not result in a higher nicotine exposure than is the case with commercially available tobacco-based snus or snus-like products that are currently common on the Scandinavian and US markets.

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 six treatment visits to the clinic, in addition to a visit for screening and a follow-up telephone visit. On the six different treatment days participants will use one of five different products of ZYN or reference /moist snuff, 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 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).

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?
August 2019 to February 2021

Who is funding the study?
Swedish Match Europe Division

Who is the main contact?
Dr Camilla Pramfalk
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
SM 19-01

Study information

Scientific Title
Nicotine plasma concentrations and pharmacokinetics of single doses of non-tobacco-based nicotine pouches (ZYN Moist and ZYN Dry Mini) and conventional, tobacco-based US moist snuff pouches among current, daily snus users

Acronym
19-01

Study objectives
The primary objective of the study is to compare the exposure of nicotine after administration of a single dose of ZYN Moist 7 mg and a single dose of Longhorn 18 mg.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/05/2020, Swedish Ethical Review Authority (Box 2110, 750 02 Uppsala, Sweden; +46 (1)104750800; registrator@etikprovning.se), Dnr 2019-06286

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

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Tobacco/nicotine use

Interventions
Investigational Product (IP), dosage and mode of administration
1. ZYN Moist Smooth containing 7 mg nicotine per portion
2. ZYN Moist Smooth containing 9 mg nicotine per portion
3. ZYN Moist Smooth containing 11 mg nicotine per portion
4. ZYN Dry Mini Smooth containing 3 mg nicotine per portion
5. ZYN Dry Mini Smooth containing 6 mg nicotine per portion

Reference product
6. Longhorn Pouch Natural containing 18 mg nicotine per portion

The participants will come for six treatment visits to the clinic, in addition to a visit for screening and a follow-up (FU) telephone visit.
On the six different treatment days participants will use one of five different products of ZYN or reference /moist snuff, 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 are followed over 6 hours after administration.

Intervention Type
Other

Primary outcome(s)
Pharmacokinetics of nicotine in plasma: the difference in AUCinf based on plasma concentrations of nicotine from 0 – 6h after administration of a single dose of ZYN Moist 7 mg and a single dose of Longhorn 18 mg, 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. Pharmacokinetics of nicotine in plasma: Tmax, Cmax, AUCinf, AUC0- 1.5h and terminal elimination half-life of the non-tobacco-based nicotine ZYN Moist pouches, ZYN Dry Mini pouches and Longhorn 18 mg. Blood samples for analysis of PK parameters will be collected pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1h, 1h:15 min, 1h:30 min, 2h, 4h, 6h post-dose. The PK parameters in the study will include AUCinf, AUC0-t, Cmax, Tmax, and terminal half-life
2. In vivo extracted amount of nicotine (mg/unit) and extracted fraction (%) 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.
3. The urge to snus, measured using a 100-mm visual analogue scale (VAS) anchored with ”not at all” to ”extremely” as answer to the question “Right now, how strong is your urge for snus?” at pre-set time points up to 60 min (-10 min pre-dose, -1 min pre-dose, 2 min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 45 min, and 60 min after each dose) after start of the investigational product (IP) administration

Completion date
01/02/2021

Eligibility

Key inclusion criteria
1. Willing and able to give written informed consent for participation in the study
2. Snus user who has used tobacco-based snus for ≥1 year, with a minimum weekly consumption of two or more snus cans, and is willing and able to usebrandsuse brands with nicotine content ≥1%
3. Healthy male or female subject aged ≥19 years
4. Women of childbearing potential (WOCBP) must be willing to use a sufficient contaceptive method for the duration of the study, this includes mechanical barrier (e.g., a male condom or a female diaphragm), combined [oestrogen 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], IUD or 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

Lower age limit
19 years

Sex
All

Total final enrolment
35

Key exclusion criteria
1. Daily smoker, defined as smoking during the last 24 hours according to self-report
2. A history or presence of diagnosed hypertension or any cardiovascular disease
3. Any surgical or medical condition, 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
4. Female subject currently breastfeeding, pregnant or planning to get pregnant during the study
5. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV)
6. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to first administration of the IP
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. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements

Date of first enrolment
31/07/2020

Date of final enrolment
12/10/2020

Locations

Countries of recruitment
Sweden

Study participating centre
CTC Clinical Trial Consultants AB
Brigadgatan 26
Linkoping
Sweden
SE-587 58

Sponsor information

Organisation
Swedish Match

Funder(s)

Funder type
Industry

Funder Name
Swedish Match Europe Division

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 3.0	01/07/2020	30/11/2022	No	No