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A study investigating the uptake to the blood circulation of nicotine from tobacco free nicotine pods compared to tobacco-based Swedish snus and American moist snuff

Submission date
03/10/2018

Recruitment status
No longer recruiting

Registration date
05/10/2018

Overall study status
Completed

Last Edited
30/11/2022

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Sweden has developed 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, is capable of rapidly delivering nicotine to the blood stream. 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.
Traditionally there has been no non-tobacco-based nicotine product on the Swedish market intended for recreational use. 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 Sweden and in the U.S. It has some features similar to snus, but ZYN® does not contain the typical unwanted substances common in snus. The toxicological safety profile of ZYN® thus represents a significant improvement over snus.
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 ZYN® products in comparison with some commercially available snus products on the Scandinavian and U.S. markets. These brands typically have a higher nicotine content and/or larger pouch size than the comparator snus product used in a previous study conducted by the

sponsor. Also, it is motivated to investigate whether the commonly used flavouring compound “wintergreen” may affect nicotine uptake, and to address the effect of pouch placement (upper versus lower lip).
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 U.S. markets.

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

What does the study involve?
On seven different days participants will use one of four different products of ZYN or three different products of snus/moist, 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 of 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 the 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 2018 to March 2019 (updated 07/04/2020, previously: January 2019)

Who is funding the study?
Swedish Match Europe Division

Who is the main contact?
Dr Mikael Staaf, mikael.staaf@swedishmatch.com

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
NA

ClinicalTrials.gov (NCT)
NA

Protocol serial number
SM 18-01

Study information

Scientific Title
Nicotine plasma concentrations and pharmacokinetics of single doses of non-tobacco-based nicotine pouches (ZYN®) compared with conventional, tobacco-based Swedish snus and American moist snuff among current, daily snus users

Acronym
18-01

Study objectives
To evaluate each subject's plasma concentrations of nicotine after administration of one single dose of ZYN® Smooth containing 6 mg of nicotine, to that of one single dose of 2x1 pouches of General PSWL Swedish snus.

Ethics approval required
Old ethics approval format

Ethics approval(s)
EPN Uppsala. Application submitted 14/09/2018.

Study design
Interventional open randomised seven-way crossover trial

Primary study design
Interventional

Study type(s)
Other

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

Interventions
Test products:
1. ZYN® Smooth containing 6 mg nicotine per portion
2. ZYN® Smooth containing 8 mg nicotine per portion
3. ZYN® Wintergreen containing 6 mg nicotine per portion
4. ZYN® Smooth containing 6 mg nicotine per portion (lower lip)
Reference products

5. Swedish portion snus, General PSWL (8 mg nicotine/g) 2 x 1.0 g
6. American moist snuff, Longhorn Pouch Natural (12 mg nicotine/g) 1.5 g
7. American moist snuff, Longhorn Pouch Wintergreen (12 mg nicotine/g) 1.5 g
The treatments are administered as single doses in a pre-determined computer-generated randomised order according to a four sequence list. The subject keeps the pouch still between the upper lip and the gum for 60 minutes. Serial plasma samples are drawn before, and at regular time intervals up to 6 hours after administration (10 samples). The duration of the treatments and follow-up for all study arms will be one day followed by 1-14 day(s) of wash-out (repeated for each dose time point) and follow-up 7 days after the last dose.

Intervention Type
Other

Primary outcome(s)
AUCinf (based on plasma concentrations of nicotine after administration of a single dose of ZYN® Smooth containing 6 mg of nicotine, to that of two doses of General PSWL Swedish snus pouches), 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 following pharmacokinetic parameters of the non-tobacco-based nicotine ZYN® Smooth pouches, General PSWL Swedish snus pouches and Longhorn American moist snuff pouches, calculated based on measurement of nicotine in blood samples with a liquid chromatography-mass spectometry (LC-MS/MS) analytical method at the completion of the study:
1.1. Tmax
1.2. Cmax
1.3. AUCinf
1.4. AUC0-t
1.5. Terminal half-life
2. Nicotine plasma concentrations for the ZYN® Wintergreen and Longhorn Wintergreen treatments compared to the corresponding non-wintergreen containing product, respectively, calculated based on measurement of nicotine in blood samples with a LC-MS/MS analytical method at the completion of the study
3. Nicotine plasma concentrations for the upper lip and lower lip placement of the non-tobacco-based nicotine pouch ZYN® Smooth, calculated based on measurement of nicotine in blood samples with a LC-MS/MS analytical method at the completion of the study
4. In vivo extracted amount of nicotine from all products, measured by subtracting the residual amount after use from the mean of 10 unused portions at completion of the study
5. Pairwise analysis of in-vitro extracted nicotine and extraction grade, measured by statistical evaluation of data at completion of the study
6. Plasma levels of Methyl salicylate for the treatments with pouches containing Wintergreen flavour, calculated based on measurement of nicotine in blood samples with a LC-MS/MS analytical method at the completion of the study
7. Adverse events measured by patient interviews during each visit

Completion date
07/03/2019

Eligibility

Key inclusion criteria
1. Snus user who have used snus for ≥1 year, with a minimum weekly consumption of two or more snus cans (brands with nicotine content ≥1%)
2. Willing and able to give written informed consent for participation in the study
3. Healthy
4. Aged 19 years or older
5. Willing and able to comply with study procedures

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
36

Key exclusion criteria
1. Smoker, defined as "smoking during the last 24 hours" according to self-report and CO in exhaled air >10 ppm at clinical visits
2. A history or presence of diagnosed hypertension or any cardiovascular disease
3. Surgery within 6 months of the screening visit that, in the opinion of the investigator, could negatively impact on the subject’s participation in the clinical study
4. Any surgical or medical condition, which, in the judgement of the clinical investigator, might interfere with the absorption, distribution, metabolism or excretion of the investigational product
5. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject’s ability to participate in the study
6. Breast feeding, pregnancy or planning to get pregnant during the study
7. Female use of systemic contraceptives (such as oral contraceptives, implants, injectable steroids, vaginal ring, transdermal patch)
8. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV)
9. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to administration of the IP
10. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse
11. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during the three months prior to screening
12. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements

Date of first enrolment
17/12/2018

Date of final enrolment
23/01/2019

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 Europe Division

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?
	results				

Results article		08/10/2020	28/05/2020	Yes	No
Participant information sheet	Participant information sheet version 3.0	11/11/2025	11/11/2025	No	Yes
Protocol file		16/01/2019	30/11/2022	No	No