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# A study investigating the uptake to the blood circulation and subjective effects of nicotine from tobacco free nicotine pods compared to tobacco based Swedish snus

**Submission date**
15/11/2017

**Recruitment status**
No longer recruiting

**Registration date**
21/11/2017

**Overall study status**
Completed

**Last Edited**
12/02/2024

**Condition category**
Other

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

## Plain English summary of protocol

Background and study aims
Sweden displays the lowest prevalence of smoking in Europe, particularly among males. Population surveys have indicated that snus is the most frequently used smoking cessation aid. Snus is a moist form of smokeless tobacco which is usually placed under the upper lip. It is sometimes used as a last resort for people who have failed stopping smoking with the available pharmaceutical smoking cessation aids. Smokeless tobacco is capable of rapidly delivering nicotine to the bloodstream, and therefore may be more satisfactory among smokers than currently available pharmaceutical nicotine products. Traditionally there has been no non-tobacco-based nicotine product on the Swedish market intended for recreational use similar to snus. Despite the vast difference in risk between snus and cigarettes in terms of adverse long-term health effects including cancer, heart disease and chronic lung disease, snus remains a controversial product as it contains tobacco and is intended for recreational use. The tobacco component of snus explains why it contains measurable amounts of hazardous constituents such as potentially carcinogenic nitrosamines, albeit at very low levels. Recently, a new non-tobacco-based nicotine product (ZYN®) has been developed. It has some features that are similar to snus: it comes in pouches with a nicotine content of 3 or 6 mg, and it is used the same way as snus, that is, it is placed under the upper lip. In contrast to snus the product contains no nitrosamines or polycyclic hydrocarbons (PAHs), which are the two main classes of unwanted substances in snus that are classified as potentially carcinogenic. Other unwanted substances in ZYN® are present in similar or lower amounts than in snus. The safety profile of ZYN® is therefore a significant improvement over snus with the exception of the nicotine content which is only marginally lower than in snus (3 or 6 mg in ZYN® versus e g 8-12 mg in a conventional 1.0 g snus pouch). Commercially available snus products have a nicotine content ranging between 1-2%. Previous studies have indicated that on average about 15-20% of the total nicotine content is extracted and absorbed, with large variations. Extraction is generally not linear with pouch size: surface area, saliva penetration and diffusion factors may determine nicotine uptake. The nicotine delivery profile of a tobacco-free product like ZYN® determines its effectiveness to function as an alternative to cigarettes and snus. In view of this, it is highly justified to study the

nicotine delivery profile of ZYN® in comparison with commercially available snus products (which have a documented ability to replace cigarettes as a source of recreational nicotine among current tobacco consumers). The sponsor has previously conducted studies of nicotine chewing gum with different nicotine content versus snus products. They now intend to extend those observations by comparing the ZYN® product with Swedish snus. The aim of this study is to measure the extraction of nicotine from ZYN® pouches and the resulting uptake to the bloodstream, compared with a conventional snus pouch.

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 five different days participants take a single dose of two different types of ZYN containing either 3 or 6 mg of nicotine, or a 1 g Swedish snus pouch containing 8 mg of nicotine. 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?
September 2017 to January 2018

Who is funding the study?
Swedish Match North Europe

Who is the main contact?
Dr Mikael Staaf

# Contact information

### Type(s)
Scientific

### Contact name
Dr Mikael Staaf

### Contact details
Maria Skolgata 83
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# Additional identifiers

### Protocol serial number
SM 17-03

# Study information

### Scientific Title
Nicotine pharmacokinetics and subjective effects of a single dose of a non-tobacco-based nicotine pouch (ZYN®) compared with conventional, tobacco-based Swedish snus among current, daily snus users

### Acronym
Uptake study

### Study objectives
To compare each subject's plasma concentration of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 or 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
EPN Uppsala, 01/11/2017, ref: Dnr 2017/433

### Study design
Single-centre open randomized five-way cross over trial

### Primary study design
Interventional

### Study type(s)
Other

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

### Interventions
1. ZYN Smooth containing 3 mg nicotine per portion
2. ZYN Smooth containing 6 mg nicotine per portion
3. ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process)
4. ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process)
5. Swedish portion snus PSWL 1.0 g (8 mg nicotine/g)

The treatments are administered as single doses in a pre-determined computer-generated randomized 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 seven days after the last dose.

### Intervention Type
Other

### Primary outcome(s)
AUCinf based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine, is calculated based on measurement of nicotine in blood samples with a LC-MS/MS analytical method at the completion of the study

### Key secondary outcome(s))
1. AUC60min, Cmax, Tmax, AUCo-t and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch is calculated based on measurement of nicotine in blood samples with a LC-MS/MS analytical method at the completion of the study
2. In-vivo extracted amount of nicotine from each portion, measured by subtracting the residual amount after use from the mean of 10 unused portions at completion of the study
3. The correlation between the estimates of AUC(inf) and the total amount of nicotine extracted from the ZYN® pouches, measured by statistical evaluation of data
4. Pulse rate and ”head buzz” (head rush, ”hit”, feeling alert, overall ”product strength”) measured using a 100-mm visual analogue scale (VAS) anchored with ”not at all” to ”extremely” at preset time points up to 60 minutes (predose, + 5min, +10 min, + 15 min, +30 min, +60 min after each dose), respectively, after study product administration (proxy for systemic uptake)
5. Adverse events measured by patient interviews

### Completion date
15/01/2018

## Eligibility

### Key inclusion criteria
1. Snus user, with a minimum weekly consumption of three or more snus cans (brands with nicotine content <1%) or two or more cans (brands with nicotine content >1%) since ≥1 year
2. Consent to participate voluntarily and sign Informed Consent Form prior to any study procedure
3. Healthy male/female, age ≥19
4. Willing and able to comply with study procedures
5. A heart rate increase ≥ 10 beats/min with first use of snus in the morning after overnight abstinence from any nicotine exposure

### Participant type(s)
Healthy volunteer

### Healthy volunteers allowed
No

### Age group

Adult

### Sex
All

### 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 judgment 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. Pregnancy or planning to get pregnant during the study
7. Positive screen for drugs of abuse at screening or on admission to the unit prior to administration of the investigational product.
8. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV)
9. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse
10. Use of any prescribed or non-prescribed medication including antacids, analgesics and herbal remedies within two weeks prior to the first administration of IP, except occasional intake of paracetamol (maximum 2 000 mg/day; and not exceeding 3 000 mg/week), at the discretion of the Investigator
11. Plasma donation within 1 month of Screening or any blood donation/blood loss >450 mL during the 3 months prior to Screening
12. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements

### Date of first enrolment
16/11/2017

### Date of final enrolment
21/11/2017

## Locations

### Countries of recruitment
Sweden

### Study participating centre
**CTC Clinical Trial Consultants AB**
Sweden
SE-752 37

# Sponsor information

### Organisation
Swedish Match North Europe

# 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? |
|---|---|---|---|---|---|
| Results article | results | 08/10/2020 | 28/05/2020 | Yes | No |
| Other unpublished results | | 28/06/2019 | 12/02/2024 | No | No |
| Protocol file | version 1.0 | 05/10/2017 | 01/12/2022 | No | No |