ISRCTN44913332 https://doi.org/10.1186/ISRCTN44913332

A study investigating the extraction of nicotine and flavors from tobacco free nicotine pods compared to tobacco based Swedish snus

Submission date
14/11/2017

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. One explanation for the record-low low smoking prevalence is that snus has replaced cigarettes as the tobacco product of choice. Snus is a smokeless tobacco capable of rapidly delivering nicotine to the bloodstream and therefore may be more satisfactory among smokers than currently available pharmaceutical nicotine products. Snus remains a controversial product as it contains tobacco and is intended for recreational use. The tobacco in snus contains carcinogenic ingredients (that could cause cancer), but at very low amounts. Recently, a novel, non-tobacco-based nicotine product (ZYN®) has been developed. It is similar to snus however it contains no nitrosamines or polycyclic hydrocarbons (PAHs) which may potentially be carcinogenic. The overall safety of ZYN® is better than snus, however it only has a little bit less nicotine than snus. When comparing the nicotine content of different nicotine-containing products, it is important to consider that the nicotine extraction and uptake varies considerably depending on product type and formulation. Commercially available snus products have a nicotine content ranging between 1-2%. Previous studies have shown that on average about 15-20% of the total nicotine content is extracted and absorbed. Extraction is generally not linear with pouch size: it is larger with small compared to larger pouches, which suggests that surface area, saliva penetration and diffusion factors may be more important determinants of nicotine uptake than pouch weight. The nicotine delivery profile of a product is probably a main determinant of its efficacy to function as an alternative to cigarettes among current smokers. The aim of this study is to measure 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).

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

What does the study involve?
The study compares the estimated in-vivo extracted dose of nicotine from a novel, non-tobacco-based nicotine pouch containing 3 or 6 mg of nicotine, with that from a 1 g Swedish snus pouch

containing 8 mg of nicotine. The study includes 14 doses of either ZYN® or snus. Participants report to the laboratory on separate days for 14 experimental interventions. All participants receive the same treatment in a randomised order. The amount of nicotine that is extracted from each dose is assessed.

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 will 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?
June 2017 to November 2017

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

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

Contact information

Type(s)
Scientific

Contact name
Dr Mikael Staaf

Contact details
Swedish Match North Europe
Maria Skolgata 83
Stockholm
Sweden
SE-118 53

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
SM 17-01

Study information

Scientific Title
The in-vivo extraction of nicotine and flavor compounds from a single dose of a non-tobacco-based nicotine pouch (ZYN®) compared with conventional, tobacco-based Swedish snus among current, daily snus users

Study objectives
The aim of this study is to compare the estimated in-vivo extracted dose of nicotine from a novel, non-tobacco-based nicotine pouch containing 3 or 6 mg of nicotine, with that from a 1 g Swedish snus pouch containing 8 mg of nicotine. Nicotine extraction may serve as a proxy for the in vivo uptake of nicotine.

Ethics approval required
Old ethics approval format

Ethics approval(s)
EPN Uppsala, 13/09/2017, ref: Dnr 2017/318

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

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Prevention

Participant information sheet
Not available in web format, only available in Swedish

Health condition(s) or problem(s) studied
Tobacco use not otherwise specified (NOS)

Interventions
The treatments are administered as single doses in a pre-determined computer-generated randomized order according to a four-sequence list. Participants are randomly allocated as to what order they receive the following doses:

1. ZYN® Smooth containing 3 mg nicotine per portion - 15 min single dose administration
2. ZYN® Smooth containing 3 mg nicotine per portion - 60 min single dose administration
3. ZYN® Smooth containing 6 mg nicotine per portion - 15 min single dose administration
4. ZYN® Smooth containing 6 mg nicotine per portion - 60 min single dose administration
5. ZYN® Smooth containing 3 mg nicotine per portion (alternative manufacturing process) - 15

min single dose administration
6. ZYN® Smooth containing 3 mg nicotine per portion (alternative manufacturing process) - 60 min single dose administration
7. ZYN® Smooth containing 6 mg nicotine per portion (alternative manufacturing process) - 15 min single dose administration
8. ZYN® Smooth containing 6 mg nicotine per portion (alternative manufacturing process) - 60 min single dose administration
9. ZYN® Wintergreen containing 3 mg nicotine per portion (Nicotine analysis) - 60 min single dose administration
10. ZYN® Wintergreen containing 3 mg nicotine per portion (Flavor analysis) - 60 min single dose administration
11. ZYN® Peppermint containing 3 mg nicotine per portion (Nicotine and Flavor analysis) - single dose 60 min administration
12. ZYN® Spearmint containing 3 mg nicotine per portion (Nicotine and Flavor analysis) - 60 min single dose administration
13. Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) - 15 min single dose administration
14. Swedish portion snus PSWL 1.0 g (8 mg nicotine/g) - 60 min single dose administration

The treatments are administered as single doses in a pre-determined randomised order. The participant keeps the pouch still between the upper lip and the gum for 15 or 60 minutes.

The total duration of the treatments and follow-up for all study arms is 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, i.e. the total duration is different depending on the number of wash-out days.

Intervention Type
Other

Primary outcome measure
Extracted dose of nicotine from each portion is measured by using GC-MS analysis and calculated by subtracting the residual amount after use from the mean of 10 unused portions. Used portions are freezed after dosing and analysis using GC-MS is performed at the end of the trial.

Secondary outcome measures
1. Pulse rate is measured using a pulsimeter at baseline, five, ten, 15, 30 and 60 minutes
2. Head buzz (head rush, “hit”, feeling alert, overall “product strength” is measured using a 100-mm visual analogue scale (VAS) at preset time points up to 30 and 60 minutes, respectively, after study product administration (as a proxy for systemic uptake)
3. The extracted dose of flavor components are measured using GC-MS analysis and calculated by subtracting the residual amount after use from the mean of 10 unused portions. Used portions are freezed after dosing and analysis using GC-MS is performed at the end of the trial.
4. Adverse events are measured using patient interviews at predose, five, ten, 15, 30 and 60 minutes

Overall study start date
02/06/2017

Completion date
14/11/2017

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. Female subjects should have a negative pregnancy test.
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

Age group
Adult

Sex
Both

Target number of participants
20

Key exclusion criteria
1. A history or presence of diagnosed hypertension or any cardiovascular disease
2. 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
3. Any surgical or medical condition, which, in the judgment of the clinical investigator, might interfere with the absorption, distribution, metabolism or excretion of the drug
4. Subjects who are pregnant

Date of first enrolment
14/09/2017

Date of final enrolment
22/09/2017

Locations

Countries of recruitment
Sweden

Study participating centre
CTC Clinical Trial Consultants AB
Akademiska Sjukhuset Ingång 85 Våning 2

Uppsala
Sweden
SE-752 37

Sponsor information

Organisation
Swedish Match North Europe

Sponsor details
Maria Skolgata 83
Stockholm
Sweden
SE-118 53

Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
Swedish Match North Europe

Results and Publications

Publication and dissemination plan
Planned publication in a peer reviewed journal.

Intention to publish date
31/12/2019

Individual participant data (IPD) sharing plan
As this is a controlled clinical trial conducted according to GCP-IHC criteria the trialists are obliged and intend to keep all study data stored after completion of the study. However, they have not yet decided where and how this will be done. The data might be shared with relevant authorities. They might potentially also share de-identified data with other researchers on an ad hoc basis. The details and logistics of such data sharing has not yet been decided.

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		15/02/2022	15/02/2022	Yes	No
Protocol file		26/06/2017	01/12/2022	No	No
Other unpublished results	clinical study report	20/12/2018	12/02/2024	No	No