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A study investigating the extraction of nicotine and flavors from tobacco-free nicotine pouches

Submission date
09/02/2021

Recruitment status
No longer recruiting

Registration date
09/02/2021

Overall study status
Completed

Last Edited
05/12/2024

Condition category
Other

[_] 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. Addition of flavors to tobacco products and e-cigarettes have been discussed by regulatory agencies during the last years. It has been suggested that some flavors could enhance nicotine uptake, which has not previously have been fully scientifically investigated for this product category. In addition, focusing on inhaled tobacco and ENDS products, WHO have highlighted that the actual levels of flavor compounds and potential metabolites delivered to the consumer is key for health risk assessment. There is a substantial inter-individual variation in uptake with products used orally which is probably related to constitutional differences in saliva production and results in a wide variation in nicotine extraction from the product. It has been postulated that some flavors could enhance nicotine uptake.
This study is a part of the effort by Swedish Match to assess the levels flavor extracted from the

products and consumers could be exposed to. The ZYN Moist products included in the current study, utilize utilize a different matrix compared to ZYN Dry products which earlier have been investigated. The nicotine extraction may differ as a consequence of different pouch geometry, water content, particle size etc. Therefore, the current study will investigate the nicotine and/or flavor extraction of ZYN Moist 9 mg products, utilizing different flavor contents, compared to an unflavored ZYN Moist product. The key goals of the study is to show equivalence of the estimated in vivo extracted fraction of nicotine between ZYN Wintergreen (1) and ZYN Smooth and to evaluate the estimated in vivo extracted amount and fraction of flavor compounds from all products after administration of one single dose.

Who can participate?
Healthy male or female volunteers aged 19 or older. All research subjects are required to be daily users of oral tobacco/nicotine products since at least one year (with an average or above snus consumption) so the participants are well acquainted with, and used to, the effects of nicotine.

What does the study involve?
The participating subjects will receive study product on 9 occasions divided into two treatment visits, in a cross-over fashion. The study will include a screening visit, two treatment visits for administration of in total 9 doses of IP, and a follow-up (FU) telephone visit.
Screening (Visit 1) will take place within 28 days prior to Visit 2 and will include an eligibility check including review of health status and evaluation of nicotine/tobacco use.
The subjects are instructed not to eat, drink, chew chewing gum, use nicotine free pouches or brush teeth from 30 minutes before and during application of the IP. Following administration of 3 or 4 doses of IP, according to a predetermined randomized order, with at least 60 minutes between doses (from end of administration to start of administration). The IPs are administered as single doses and the subject keeps the pouch still between the upper lip and the gum for 60 minutes and are instructed not to manipulate the pouch with the tongue or lips. After 60 minutes the pouches are collected and frozen (-20°C) pending analysis of residual nicotine and flavor compound content.

What are the possible benefits and risks of participating?
There are no possible benefits to participating. 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?
May 2020 to June 2021 (updated 01/04/2021, previously: March 2021)

Who is funding the study?
Swedish Match North Europe (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

Protocol serial number
SM 20-01

Study information

Scientific Title
In vivo extraction of nicotine and flavor compounds from a single dose of non-tobaccobased nicotine pouches (ZYN Moist)

Acronym
SM 20-01

Study objectives
The overarching aim of the study is to evaluate if the different flavor components have an impact on the nicotine extraction from a ZYN Moist 9 mg product compared to an unflavored ZYN Moist 9 mg product. In addition, the extraction of selected flavor components will be determined.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/01/2021, Swedish Ethics Review Appeals Board (Swedish Research Council. Box 1035 101 38 Stockholm, Sweden; no telephone number provided; Kansli@onep.se), ref: Dnr Ö 72-2020/3.1
Application EPN Dnr 2020-03872

Study design
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
Tobacco/nicotine use

Interventions
Investigational Product (IP) and dosage (oral smokeless nicotine pouch)
ZYN Moist Wintergreen (1)* containing 9 mg nicotine/pouch
ZYN Moist Wintergreen (2)* containing 9 mg nicotine/pouch
ZYN Moist Chill containing 9 mg nicotine/pouch
ZYN Moist Cool Mint containing 9 mg nicotine/pouch
ZYN Moist Citrus containing 9 mg nicotine/pouch
ZYN Moist Spearmint containing 9 mg nicotine/pouch
ZYN Moist Deep Freeze containing 9 mg nicotine/pouch
ZYN Moist Smooth containing 9 mg nicotine/pouch
*ZYN Moist Wintergreen product (1) and (2) contains a different amount of the flavor wintergreen

The participating subjects will receive the study product on 9 occasions divided into two treatment visits, in a cross-over fashion, with 60 minutes of treatment per occasion.
Each subject will participate in the study for a period of approximately 5 weeks (including a screening period of up to 4 weeks).

Intervention Type
Other

Primary outcome(s)
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.

Key secondary outcome(s))
1. 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 study
2. Self-report of potential adverse events (AEs, frequency, intensity and seriousness) measured throughout the study

Completion date
15/06/2021

Eligibility

Key inclusion criteria
1. Willing and able to give written informed consent for participation in the study
2. Male or female subject aged ≥19 years

3. Subject who has used oral tobacco/nicotine products for ≥1 year, with a minimum daily consumption of five or more snus pouches, and is willing and able to use brands with nicotine content ≥1%
4. Women of child bearing potential (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 [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. 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 of the IP 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
2. Any clinically significant illness in the 28 days prior to the first IP administration
3. A history or presence of untreated diagnosed hypertension or any cardiovascular disease
4. Female subject currently breast feeding, pregnant or planning to get pregnant during the study
5. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to first administration of the IP
6. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the Investigator
7. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements

Date of first enrolment
27/01/2021

Date of final enrolment
05/02/2021

Locations

Countries of recruitment
Sweden

Study participating centre
CTC Clinical Trial Consultants AB (CTC)
Uppsala University Hospital
Entrance 85, 2nd level
Uppsala
Sweden
SE-751 85

Study participating centre
CTC Clinical Trial Consultants AB (CTC)
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 datasets generated during and/or analysed during the current study are available from the corresponding author Dr Erik Lunell (croelab@gmail.com) or the last author Robert Pendrill (robert.pendrill@swedishmatch.com) on reasonable request.

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 1.0	24/06/2020	30/11/2022	No	No