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Effects of flavors in oral tobacco-derived nicotine pouches on nicotine exposure

Submission date
03/11/2021

Recruitment status
No longer recruiting

Registration date
13/12/2021

Overall study status
Completed

Last Edited
03/12/2024

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] 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 males and some females.
Nicotine is the substance that is the major contributor to the addictive properties of tobacco products, and nicotine exposure may contribute to adverse pregnancy outcomes. Despite the vast risk 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. The tobacco component of snus explains why it contains measurable amounts of unwanted potentially carcinogenic substances, albeit at very low concentrations.
Oral tobacco-derived nicotine (OTDN) products (such as ZYN) have been commercially available for a few years. They have some features that are similar to snus as 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 (1.5 – 13 mg/unit) is comparable to that in snus and many other oral tobacco products that are currently common on the market in Scandinavia and the US, which have nicotine contents ranging from 3 mg/unit to more than 20 mg/unit.
When comparing the nicotine content of different nicotine-delivery products it is important to consider that the nicotine extraction and uptake varies considerably depending on the product type (tobacco vs a non-tobacco-based matrix) and product formulation (pouch geometry, water content, particle size, pH, etc). In addition, there is a substantial variation between people in uptake for products used orally, which is probably related to differences in saliva production and results in a wide variation in nicotine extraction.
While many OTDN products are currently commercially available, only a limited number of these products have so far been scientifically tested. It has been suggested that some flavors may enhance nicotine uptake, which has not been fully scientifically investigated for this product category. Similarly, there is a lack of scientific data regarding any possible impact of flavors on pharmacodynamic parameters (the response of the body to nicotine). This study is part of the efforts by Swedish Match to assess if flavor affects nicotine uptake, pharmacokinetics (what the body does to nicotine), and pharmacodynamics of ZYN Dry products. The overarching aim of the study is to ensure that the flavored ZYN Dry products do not cause a higher nicotine exposure than the equivalent unflavored ZYN Dry Smooth product.

Who can participate?:
Healthy male or female volunteers aged 21 years or older who have used oral tobacco/nicotine products for more than 1 year

What does the study involve?:
The participants visit the clinic for a screening visit (Visit 1) followed by nine treatment visits (Visit 2-10) on separate days. Screening (Visit 1) takes place within 4 weeks before Visit 2. On Visit 2, the participants are randomly allocated to one of six treatment sequences. On the nine different treatment days participants use one of nine different products, including the comparator product. The treatments are 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 measured for 6 hours after dose administration.

What are the possible benefits and risks of participating?:
There are no direct benefits for participants, aside from a brief medical examination providing information about their general state of health. Hence, the safety and wellbeing of the subjects are of utmost importance. Similar products are commercially available and only participants who are well acquainted with and used to the effects of nicotine can participate in the study. The only side effects are the effects likely to be related to nicotine exposure (such as salivation, nausea, headache, and dyspepsia [indigestion]).

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?:
October 2021 to June 2022

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

Who is the main contact?:
Dr Camilla Pramfalk
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
SM21-01

Study information

Scientific Title
Nicotine plasma concentrations, pharmacokinetics, and pharmacodynamics following single doses of flavored oral tobacco-derived nicotine pouches in current, daily oral tobacco/nicotine users

Acronym
SM21-01

Study objectives
The study hypothesis is that the flavored ZYN Dry products do not entail a higher nicotine exposure than the equivalent unflavored ZYN Dry product.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/11/2021, Swedish Ethical Review Authority, Gothenburg Section 1 Medicine (Etikprövningsmyndigheten, Box 2110, 75002, Uppsala, Sweden; +46 (0)104750800; registrator@etikprovning.se), ref: Dnr 2021-05945-01

Study design
Single-center open-label randomized nine-way cross-over single-dose administration study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

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

Interventions
Investigational product (IP) and dosage (oral smokeless nicotine pouch):
ZYN Dry Smooth, containing 6 mg nicotine per pouch (unflavored comparator product)
ZYN Dry Virginia Blend, containing 6 mg nicotine per pouch
ZYN Dry Kentucky Bold, containing 6 mg nicotine per pouch
ZYN Dry Cherry, containing 6 mg nicotine per pouch
ZYN Dry Dragonberry, containing 6 mg nicotine per pouch
ZYN Dry Peach, containing 6 mg nicotine per pouch
ZYN Dry Wine, containing 6 mg nicotine per pouch
ZYN Dry Bourbon, containing 6 mg nicotine per pouch
ZYN Dry Dark Rum, containing 6 mg nicotine per pouch

The study subjects visit the clinic for a screening visit (Visit 1) followed by nine treatment visits (Visit 2-10) on separate days. Screening (Visit 1) takes place within four weeks prior to Visit 2. On Visit 2, the subjects are randomized to one of six treatment sequences. As this is an open-label study, the treatment sequence to which each subject is allocated is recorded in the electronic case report form (eCRF). A computer-generated randomization list is created using SAS Proc Plan, SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC), containing the subject number, treatment sequence, period, and treatment. The treatments (IPs) are administered as single doses in a pre-determined randomized order.

The study subjects keep the pouch still between the upper lip and the gum for 60 minutes. Pharmacokinetics of nicotine in plasma, pulse rate and subjective parameters will be followed for 6 hours after administration. Each subject will participate in the study for a period of approximately 5 weeks, not including the preceding 4-week screening period.

Intervention Type
Other

Primary outcome measure
The equivalence (90% confidence interval between 0.8 and 1.25) in AUCinf based on nicotine plasma concentrations from 0 to 6 hours after the administration of single doses of unflavored ZYN Dry Smooth and flavored ZYN Dry Virginia Blend, calculated based on measurement of nicotine in blood samples with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method at the end of the study

Secondary outcome measures
1. The difference in in vivo extracted amount (mg/unit) and extracted fraction (%) of nicotine between the unflavored ZYN Dry Smooth and the flavored ZYN Dry products analyzed at t=60 min (removal of pouch). The in vivo extraction of nicotine is calculated by subtracting the residual amount after use from the mean of 10 unused pouches. Used pouches are frozen and analyzed using gas chromatography mass spectrometry (GC-MS) at the end of the study
2. Pharmacokinetics of nicotine in plasma: The equivalence between the unflavored and flavored ZYN Dry products in the non-adjusted and baseline-adjusted pharmacokinetic parameters Cmax

and AUCinf based on plasma concentrations of nicotine after the administration of single doses, calculated based on measurement of nicotine in blood samples with a liquid chromatography-mass spectrometry (LC-MS/MS) analytical method at the end of the study. Blood samples for analysis of pharmacokinetic parameters are collected up to 6 hours after IP administration (-10 min pre-dose, and 5 min, 10 min, 15 min, 30 min, 45 min, 1h, 1 h:15 min, 1 h:30 min, 2 h, 4 h, 6 h post-dose)
3. Pharmacokinetics of nicotine in plasma: The difference between the unflavored and flavored ZYN Dry products in the non-adjusted and baseline-adjusted pharmacokinetic parameters Tmax, AUC0-1.5h, and AUC0-last, measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method at pre-defined timepoints: pre-administration (within 15 min prior to dose), and 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, 1 h:15 min, 1 h:30 min, 2 h, 4 h, and 6 h post-administration.
4. The difference between the unflavored and flavored ZYN Dry products for the highest recorded increase in pulse rate from baseline, measured using a pulse oximeter at pre-defined time points up to 6 hours after IP administration (-10 min pre-dose, and 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h:15 min, 1h:30 min, 2 h, 4 h, 6 h post-dose)
5. The difference between the unflavored and flavored ZYN Dry products for the highest recorded increase in the subjective parameters “craving” and “satisfaction”, measured using a 100-mm visual analogue scale (VAS) at pre-defined time points up to 6 hours after IP administration (-10 min pre-dose, and 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1 h:15 min, 1 h: 30 min, 2 h, 4 h, 6 h post-dose)
6. The differences between the unflavored and flavored ZYN Dry products for the subjective parameters “product-liking” and “intent to use again”, measured using a 100-mm visual analogue scale (VAS) 1 hour after IP administration
7. Frequency, intensity, and seriousness of adverse events (AEs) will be collected by subject interview from the start of IP administration (Visit 2) until the last treatment visit (Visit 10). The grading of the intensity of AEs will follow the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Overall study start date
01/10/2021

Completion date
30/06/2022

Eligibility

Key inclusion criteria
1. Willing and able to give written informed consent for participation in the study
2. Subjects who have used oral tobacco/nicotine products for ≥1 year, with a minimum daily consumption of five or more pouches, and who are willing and able to use products with nicotine content ≥1 %
3. Healthy male or female subject aged ≥21 years
4. Clinically normal medical history, physical findings, vital signs, ECG, and laboratory values at the time of screening, as judged by the Investigator
5. Female subjects of child-bearing potential 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 [estrogen 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], intrauterine device (IUD) or intrauterine system (IUS). Sexual abstinence is allowed when this is the preferred and usual lifestyle of the subject

Participant type(s)
Healthy volunteer

Age group
Adult

Sex
Both

Target number of participants
Approximately 63 subjects will be screened with the aim to achieve 42 randomized subjects and 36 fully evaluable subjects.

Total final enrolment
42

Key exclusion criteria
1. A history of diagnosed hypertension or any cardiovascular disease, or ongoing manifestations of hypertension or any cardiovascular disease as judged by the Investigator
2. 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, distribution, metabolism or excretion 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
3. Subjects who are pregnant, breastfeeding, or intend to become pregnant during the course of the study
4. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV)
5. A history of diagnosed severe allergy/hypersensitivity or ongoing manifestations of severe allergy/hypersensitivity to aroma compounds (including fragrances and/or flavorings), as judged by the Investigator
6. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to first IP administration. Positive results that are expected given the subject's medical history and prescribed medications can be disregarded as judged by the Investigator
7. Current, ongoing use of beta-adrenergic blocking agents (beta-blockers), including pro re nata (as needed) use
8. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the Investigator
9. Plasma donation within 1 month of screening or blood donation (or corresponding blood loss) during the 3 months prior to screening
10. Subjects who intend to change their nicotine consumption habit, including the intention to stop using nicotine products, within the next 3 months from the screening visit, as judged by the Investigator
11. The Investigator considers the subject unlikely to comply with study procedures, restrictions, and requirements

Date of first enrolment

10/01/2022

Date of final enrolment
16/02/2022

Locations

Countries of recruitment
Sweden

Study participating centre
CTC Clinical Trial Consultants AB
Dag Hammarskjölds väg 10B
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Sponsor information

Organisation
Swedish Match North Europe AB

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Sponsor type
Industry

Website
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Funder(s)

Funder type
Industry

Funder Name

Results and Publications

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

Intention to publish date
30/06/2025

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 1.0	29/10/2021	30/11/2022	No	No