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Effects on oral health from the usage of ZYN Dry and ZYN Moist nicotine pouches

Submission date
13/07/2022

Recruitment status
No longer recruiting

Registration date
01/09/2022

Overall study status
Completed

Last Edited
09/06/2025

Condition category
Oral Health

[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:
Snus is a tobacco-based product which has been used for a long time in Sweden. No increased caries risk is associated with snus use and no difference in terms of filled teeth has been found when comparing matched Swedish adolescent snus users and non-users. Instead, it has been reported that tobacco-based snus products can reduce biofilm acidogenicity and thus may protect against dental caries. This contrasts with American snuff and other smokeless products, which have been found to increase the risk of dental caries. Gingival hyperplasia, known as snus-induced lesions, are commonly found among tobacco-based snus users. Tobacco-products (e.g., cigarettes and some smokeless tobacco products) have also been reported to affect other periodontal tissues such as cementum, alveolar bone, and the periodontal ligament and to be associated with periodontal disease.
During the last few years, the market for non-tobacco-leaf containing products, such as nicotine pouches (NPs), have grown tremendously and NP products are now sold under several brand names such as ZYN, VOLT, LYFT, VELO, and ON!. ZYN is available in two types of product categories, ZYN Dry and ZYN Moist, and comes in various flavors and nicotine strengths. 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 United States. 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 product type (tobacco vs. a non-tobacco-based matrix) and product formulation (pouch geometry, solubility, water content, particle size, pH, etc.). In addition, there is a substantial interindividual variation in uptake for products used orally, which is probably related to constitutional differences in saliva production, for example, and results in a wide variation in nicotine extraction. Previous studies have found that tobacco-based snus (General portion snus white large) and ZYN Dry release approximately 32-33% and 50-60% of the nicotine during 60 min, respectively, although with large interindividual variation. Other studies have found that ZYN Moist (also called ZYN ULTRA), which has a larger pouch dimension and higher moisture, salt, and nicotine content than ZYN Dry, releases approximately 32-42% of the nicotine during 60 min.
A previous clinical oral health study, in which healthy, current daily snus users were recommended to replace as much as possible of their snus with ZYN Dry during the 6-week study period, found that use of ZYN Dry is less harmful to the soft tissue and causes less snus-induced lesions. However, limited information is still present regarding ZYN´s effect on the oral

environment, specifically variables related to dental caries and periodontal disease. The overarching aim of the study is to clinically evaluate the effects on dental plaque acidogenicity and other oral variables in current, daily users of tobacco-based snus who completely substitute their snus use with either ZYN Dry or ZYN Moist.

Who can participate?
Healthy male or female tobacco-based snus users aged between 21 and 55 years who have used tobacco-based snus for less than 1 year, and have a minimum weekly consumption of 3 or more cans.

What does the study involve?
The study subjects visit the clinic for a screening visit (Visit 1), 5 weeks before treatment with one of the study products, followed by 4 assessment visits (Visit 2: 28 days before allocation to treatment, Visit 3: the day treatment begins, Visit 4: 14 days after treatment began, and Visit 5: 28 days after treatment began). Up until Visit 3, the subjects continue using their regular tobacco-based snus product. After the study assessments on Visit 3, the subjects are allocated at random to one of two treatment groups, with an equal chance of being in either group (like tossing a coin), in which they substitute their regular tobacco-based snus product with either ZYN Dry or ZYN Moist NPs. In both groups, the subjects can choose between three flavours, depending on their preferences. The NPs are used for four weeks, following the subject´s regular pattern of use. Oral health, as well as safety and tolerability of the NPs will be assessed in the study. Each subject will participate in the study for a period of eight weeks, not including the preceding screening period.

What are the possible benefits and risks of participating?
There are no direct benefits for the subjects to participate in the study, aside from an oral examination, which may provide them with information on their general state of oral health. Hence, the safety and well-being of the subjects are of utmost importance. Similar products are currently commercially available and only adult participants who are well acquainted with and used to the effects of nicotine can participate in the study. So far, no adverse events (AEs) have been reported in previous pharmacological clinical studies with similar products, apart from effects likely to be related to nicotine exposure (such as salivation, nausea, headache, and indigestion).

Where is the study run from?
The study is sponsored by Swedish Match North Europe (Sweden) and will be run from the University of Gothenburg (Sweden)

When is the study starting and how long is it expected to run for?
March 2022 to May 2023

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

Who is the main contact?
Dr Camilla Pramfalk, camilla.pramfalk@swedishmatch.com

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
SM22-01

Study information

Scientific Title
Effects of two types of nicotine pouch (NP) products on oral health, specifically focusing on dental caries, soft tissues, and periodontal health in current, daily tobacco-based snus users transitioning to NPs

Acronym
SM22-01

Study objectives
The changes in dental plaque acidogenicity after four weeks of tobacco-based snus substitution do not differ between ZYN Dry and ZYN Moist nicotine pouches.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/08/2022, Swedish Ethical Review Authority, Stockholm Section 4 Medicine (Etikprövningsmyndigheten, Box 2110, 75002, City: Uppsala, Sweden; +46 (0)104750800; registrator@etikprovning.se), ref: Dnr 2022-03919-01

Study design
Single-center open-label two-armed randomized longitudinal study

Primary study design

Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Impact of nicotine use on oral health, dental caries

Interventions
Investigational products (IPs) to choose from in treatment arm 1:
ZYN Dry Smooth, containing 6 mg nicotine per pouch
ZYN Dry Cool Mint, containing 6 mg nicotine per pouch
ZYN Dry Citrus, containing 6 mg nicotine per pouch

IPs to choose from in treatment arm 2:
ZYN Moist Smooth, containing 9 mg nicotine per pouch
ZYN Moist Cool Mint, containing 9 mg nicotine per pouch
ZYN Moist Citrus, containing 9 mg nicotine per pouch

The study subjects visit the clinic for a screening visit (Visit 1) followed by 4 treatment visits (Visit 2-5, Day -28, Day 0, Day 14, and Day 28). The screening (Visit 1) takes place within 5 weeks prior to Visit 2. Up until Visit 3 (Day 0) the subjects continue using their regular tobacco-based snus product. After the study assessments on Visit 3, the subjects are randomized to one of two treatment arms in which they substitute their regular tobacco-based snus product with either ZYN Dry or ZYN Moist nicotine pouches. The subjects can choose between three IPs, depending on flavor preferences, within each treatment arm. As this is an open-label study, the treatment arm to which each subject is allocated is recorded in the electronic case report form (eCRF). A computer-generated randomization list is created, containing subject number, treatment sequence, period, and treatment. The nicotine pouches are used ad libitum for four weeks, following their regular pattern of use. Dental plaque acidogenicity, number of cariogenic microorganisms, amount of plaque, degree of oral mucosal lesions, tooth discoloration, biomarkers of exposure in urine and saliva, as well as safety and tolerability will be assessed in the study. Each subject will participate in the study for a period of eight weeks, not including the preceding screening period.

Intervention Type
Other

Primary outcome(s)
The difference in dental plaque acidogenicity measured using pH in plaques on two buccal surfaces in the upper jaw, one approximal surface in the upper jaw, and one approximal surface in the lower jaw before and up to 60 min after a 1 min mouth rinse with 10 mL of a 10% sucrose solution at -28, 0, 14, and 28 days

Key secondary outcome(s))
1. The difference in dental plaque acidogenicity measured using pH in plaques at -28, 0, 14, and 28 days
2. The difference in the counted number of cariogenic microorganisms in dental plaque measured using a count of the number of colony-forming units of pooled plaque samples collected with a sterile toothpick from buccal areas and plated on agar plates for analyses of the number of microorganisms related to caries and periodontal diseases (and for assessment of

gene expression levels to analyse a broader range of cariogenic microorganisms) at -28, 0, 14, and 28 days
3. The difference in the amount of plaque measured using a count of the amount of plaque on all surfaces of the Ramfjord teeth (16, 21, 24, 36, 41, and 46) and scoring 0-3 of six sites of each tooth for plaque at -28, 0, 14, and 28 days
4. The difference in the degree of oral mucosal lesions by presence, visual grading, and histopathological evaluation of biopsies measured using:
4.1. Assessment and grading (1-4) of gingival hyperplasia from visual assessment and clinical photos taken at -28, 0, 14, and 28 days
4.2. Histopathological evaluation and diagnosis of punch biopsy (4 mm in diameter, fixed in 10% formaldehyde, processed, mounted on glass slides, and stained) from the oral mucosa, where the pouch previously was placed, collected at 0 and 28 days
5. The difference in tooth discoloration, measured using a colorimeter and by visual shade grading using a shade guide of the maxillary and mandibular anterior teeth performed at -28, 0 (before and after cleaning the teeth with rotating rubber cup and polishing paste), and 28 days
6. Safety measured using the frequency, intensity, and seriousness of adverse events (AEs) collected by subject interview between 0 (the start of IP administration, Visit 3) and 28 (the last treatment visit, Visit 5) days

Completion date
22/05/2023

Eligibility

Key inclusion criteria
1. Willing and able to give written informed consent for participation in the study.
2. Have used tobacco-based snus for ≥1 year, with a minimum weekly consumption of ≥3 cans, and ≥90% of the total nicotine consumption should have been tobacco-based snus
3. Non-smoker (have smoked ≤5 packages in total ever and have not smoked at all during the last year)
4. Healthy male or female subject aged ≥21 to ≤55 years
5. Normal stimulated salivary secretion rate (>0.7 ml/min)
6. At least 24 own teeth remaining and overall good oral health, as judged by the Investigator
7. 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), intra uterine device (IUD) or intra uterine system (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

Sex

All

Total final enrolment
45

Key exclusion criteria
1. 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. 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
5. Severe oral conditions such as open caries lesions, severe periodontal health, lesions in the soft tissues (apart from gingival hyperplasia related to the use of snus), or extensive prosthetic work (e.g. several implants, partial denture, dental veneers).
6. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the Investigator
7. Antibiotic use ≤4 weeks prior to the screening period
8. Subjects who intend to change their nicotine consumption habit, including the intention to stop using nicotine products, within the next 4 months of the screening visit, as judged by the Investigator
9. Subjects undergoing other dental treatment during the study period
10. The Investigator considers the subject unlikely to comply with study procedures, restrictions, and requirements

Date of first enrolment
10/11/2022

Date of final enrolment
16/02/2023

Locations

Countries of recruitment
Sweden

Study participating centre
Department of Cariology, Institute of Odontology
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University of Gothenburg
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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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 1.1	09/09/2022	30/11/2022	No	No