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A study characterizing nicotine uptake to the bloodstream from novel tobacco-free oral nicotine pouches compared to Swedish portion snus and nicotine gum

Submission date
14/01/2021

Recruitment status
No longer recruiting

Registration date
28/01/2021

Overall study status
Completed

Last Edited
25/11/2024

Condition category
Other

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

Plain English summary of protocol

Background and study aims

In recent years, new forms of nicotine-containing but non-combustible products have been developed, tested and marketed. These products may have the potential to reduce the human body's exposure to harmful compounds present in tobacco and/or cigarette smoke. Since July 2018, Nordic Spirit, a novel tobacco-free oral nicotine pouch, has been manufactured and sold in Sweden and has since expanded distribution in other EU countries and the UK.

Tobacco-free oral nicotine pouches are an alternative choice to both combusted or non-combusted tobacco products. They are also an alternative choice for users of smokeless tobacco such as snus (Article 2 of the EU TPD2 Directive defines smokeless tobacco products as those "not involving a combustion process, including chewing tobacco, nasal tobacco and tobacco for oral use"). Nordic Spirit contains a blend of plant-based fibers, a gum base, additives and flavorings used in the food industry, and Nicotine Polacrilex (20%) which is a resin containing pharmaceutical grade nicotine. All the ingredients are packed into a small pouch and nicotine is absorbed through the gum when the pouch is placed under the lip.

In Sweden, there is a long history of snus use. Swedish snus is a moist, ground oral smokeless tobacco product. The pouch size and shape of Nordic Spirit are similar to those of Swedish portion snus and the product is used in the same way (placed under the lip). The nicotine content of Nordic Spirit products is 11.2 mg, 9 mg and 6 mg per pouch, similar to those seen in general Swedish portion snus.

The adverse effects of nicotine have been well documented in clinical studies for a variety of tobacco products including Swedish snus, combustible cigarettes and nicotine replacement therapy medication (NRT) such as nicotine gum. Nicotine can cause short-term effects such as increased blood pressure, rapid heart rate, and dizziness. At high levels, nicotine is toxic but not at the levels typically obtained in combusted or non-combusted tobacco products. During NRT use, certain adverse effects such as nausea, vomiting, palpitation, dizziness and headache have been recorded in relation to nicotine overdose, but these effects were very rare and most were mild. Other known adverse effects of nicotine in tobacco or other nicotine-containing products include stomach and/or intestinal discomfort and irritation of the mouth.

The aim of this study is to assess the nicotine delivery and other potential side effects of Nordic Spirit products following a single use of three products in healthy adult users of Swedish portion snus. Comparison products will be Swedish portion snus and NRT (nicotine gum). This study will assess nicotine delivery and the effects of nicotine following the use of the products, including changes in blood pressure and pulse rate, user experience and adverse events.

Who can participate?
Healthy volunteers aged 19-64 who currently use Swedish portion snus and have done for at least 6 months

What does the study involve?
Eligibility to participate in the study will be checked at the screening visit (Visit 1). At Visits 2 to 6, eligible subjects will arrive at the research clinic in the morning and remain at the clinic for about 10 hours for investigational product use and blood sampling, safety assessments, assessment of changes in vital signs, and self-assessment of product experience. Participants will be randomly allocated to one of ten study groups and use each of the five investigational products once on each day of Visits 2 to 6 . The subjects will not use snus or any other nicotine-containing products for at least 12 hours before the start of each visit. There will be at least 24 hours between each visit. A follow-up telephone call will be made 6-8 days after the last product use.

What are the possible benefits and risks of participating?
Participants will have physical examinations and access to the results of their laboratory tests, so they may gain further knowledge about their general health and potentially identify any unknown medical conditions. Participants are required to be daily snus users for at least 6 months, so that participants are well acquainted with, and used to, the effects of nicotine. As such, participants will not be exposed to any increased health risks compared to their daily use of snus. The potential adverse effects from using the study products, which are commercially available, are likely to be minor and similar with known effects of tobacco/nicotine exposure (such as nausea, vomiting, palpitation, dizziness and headache). However, any adverse effects that occur in the study will be carefully monitored and documented. Aside from the risks related to the study product as described above, there may be risks related to the use of certain study medical devices e.g. indwelling venous catheters used for blood sampling. However, such devices are routinely used in medical care and the risk associated with their use is considered low. Some study procedures, like blood-pressure measurements using a blood pressure cuff and blood-sampling, may cause discomfort.

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?
February 2020 to March 2021

Who is funding the study?
JT International SA (Switzerland)

viii. Who is the main contact?
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Contact information

Type(s)
Scientific

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EudraCT/CTIS number
2020-003150-68

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
JTIG-2001-SE

Study information

Scientific Title
A randomized, open-label, crossover study to characterize nicotine pharmacokinetic parameters following the use of novel nicotine-containing products (Nordic Spirit) for oral use compared to Swedish portion snus and nicotine gum, in healthy adult snus users

Study objectives
To characterize nicotine pharmacokinetic parameters following the use of three variants of novel nicotine-containing products for oral use, compared to conventional Swedish portion snus and nicotine gum.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/12/2020, Swedish Ethical Review Authority (Linköping Department of Medicine, Etikprövningsmyndigheten, Box 2110, 750 02 Uppsala, +46 (0)10-475 08 00; registrator@etikprovning.se), ref: Dnr 2020-05745

Study design

Open-label randomized single-investigational product use five-period ten-sequence crossover 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 uptake

Interventions
Subjects will be randomly assigned to one of ten sequences and use each of the following five investigational products once in accordance with the assigned sequence.

Test products:
1. Nordic Spirit containing 6 mg nicotine/pouch
2. Nordic Spirit containing 9 mg nicotine/pouch
3. Nordic Spirit containing 11.2 mg nicotine/pouch
Comparator products:
4. Conventional Swedish portion snus (LD Original Vit Stark portion) 11.2 mg nicotine/pouch
5. Nicotine gum (Nicorette, mint flavor gum) containing 4 mg nicotine/gum

For the Nordic Spirit or the conventional Swedish portion snus, subjects will be asked to place a pouch between the upper lip and gum and keep it there for 30 minutes. For the nicotine gum, subjects will be asked to chew the gum slowly ad libitum for 30 minutes, with pauses during which the gum will be rested in the mouth.

Intervention Type
Other

Primary outcome measure
Plasma nicotine levels will be analyzed for the pharmacokinetic parameters (maximum plasma concentration [Cmax], time to Cmax [Tmax], area under the concentration versus time curve from time point zero to time point 60 minutes [AUC0-60] and AUC from time zero to the last time point with a measurable concentration [AUC0-last] following a single use) using blood samples which will be collected up to 10 minutes before investigational product use and at 5, 8, 10, 15, 20, 30, 45 minutes, and 1, 1.5, 2, 3, 4, 6 and 8 hours after the start of investigational product use.

Secondary outcome measures
1. Changes in vital signs (blood pressure and pulse rate) from the baseline will be measured at 5, 30 and 60 minutes after the start of investigational product use
2. Subjective effects (including satisfaction, psychological reward, aversion and relief) will be measured using a modified version of the Product Evaluation Scale following a single use of the investigational product
3. Intent to use the product again will be measured using the Intent to Use the Product Again Questionnaire (visual analogue scale) following a single use of investigational products
4. The amount of nicotine delivered from Nordic Spirit products 6 mg, 9 mg and 11.2 mg and conventional Swedish portion snus will be measured following a single use of investigational products. The difference between the nicotine content of the unused/reference pouch and the pouch used in the study will be used to calculate the delivered amount of nicotine

Overall study start date
21/02/2020

Completion date
09/03/2021

Eligibility

Key inclusion criteria
1. Willing and able to give written informed consent for participation in the study
2. Healthy male or female subject aged 19-64 years inclusive
3. Body Mass Index (BMI) ≥18.5 and ≤30.0 kg/m² at screening
4. Subject who currently use factory-made Swedish portion snus (nicotine content ≥8 mg per pouch) daily (≥1 snus pouch per day, 7 days per week) and who indicate that they have used such snus continuously for at least six months prior to screening
5. Positive urine cotinine test (>200 ng/ml) at screening
6. Clinically normal medical history, physical findings, vital signs, ECG and laboratory values at the time of screening, as judged by the Investigator
7. Women of childbearing 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

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
30

Total final enrolment
30

Key exclusion criteria
1. 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
2. Any clinically significant illness, medical/surgical procedure or trauma within 2 weeks of the first visit for the outcomes assessments
3. Malignancy within the past 5 years with the exception of in situ removal of basal cell carcinoma
4. Any surgery within 6 months of the screening visit that could negatively impact on the subject's participation, as judged by the Investigator
5. Any planned major surgery within the duration of the study
6. Medical history of seizures (single occasions of febrile seizure in the childhood excluded)
7. Clinically significant liver disease, as judged by the Investigator, and/or an elevation in total bilirubin, alkaline phosphatase, LDH, AST, or ALT of >3 times the upper limit
8. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C virus antibodies and HIV
9. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to any use of the IP
10. Systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg, after 10 min supine rest
11. Poor peripheral venous access, as judged by the Investigator
12. Female subjects who are pregnant or who are currently breastfeeding
13. History of alcohol abuse or excessive intake of alcohol, as judged by the Investigator
14. Presence or history of drug abuse and/or anabolic steroids, as judged by the Investigator
15. Subjects who have used any tobacco/nicotine-containing products (including electronic cigarettes, heat-not-burn products, nicotine pouches etc) or NRT medications, other than factory-made Swedish portion snus within 14 days of screening. (A single occasional use of conventional cigarettes within the 14 days prior to screening is allowed)
16. Subjects who, prior to enrolment, are planning to quit tobacco use during the study period or are postponing a quit attempt in order to participate in the study. All subjects will be informed that they are free to quit tobacco use and withdraw from the study at any time
17. Any use of prescription or over-the-counter bronchodilator medication (e.g. inhaled or oral β-adrenergic agonists) to treat a chronic condition within the 12 months prior to the first visit for the outcomes assessments
18. Any medication (prescription or over-the-counter [OTC]) within 14 days or within 5 half-lives of the drug (whichever was longer) prior to the first visit for the outcomes assessments, which has an impact on CYP2A6 activity
19. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during the three months prior to screening
20. Planned treatment or treatment with another investigational product within 3 months prior to the first visit for the outcomes assessments. Subjects consented and screened but not dosed in previous phase I studies are not excluded
21. Subjects who are employed by the tobacco industry, the clinical site, or handle unprocessed tobacco as part of their job
22. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements

Date of first enrolment
11/01/2021

Date of final enrolment
01/02/2021

Locations

Countries of recruitment
Sweden

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

Organisation
JT International SA

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
JT International SA

Results and Publications

Publication and dissemination plan
1. Additional documents not currently available
2. Planned publication of the data at a scientific conference or in a peer-reviewed journal after the clinical study report is finalized

Intention to publish date
09/03/2022

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		23/11/2024	25/11/2024	Yes	No