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# A study measuring nicotine uptake to the bloodstream from novel tobacco-free oral nicotine pouches compared to combustible cigarettes and nicotine gum

**Submission date**
05/01/2022

**Recruitment status**
No longer recruiting

**Registration date**
22/04/2022

**Overall study status**
Completed

**Last Edited**
05/06/2024

**Condition category**
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

## Plain English summary of protocol

Background and study aims
In recent years, tobacco-free nicotine pouch products have shown significant market expansion globally and increases in the number of different brand variants available. However, only a limited number of these tobacco-free nicotine pouch products have, thus far, been clinically assessed to determine their safety more accurately during human use.
Firstly, there is a lack of information in terms of the potential impact of nicotine pouches on smokers. Nordic Spirit is an alternative for combusted tobacco products, including combustible cigarettes. So far, the health impacts of nicotine pouches on smokers has been assessed in a clinical study in which the nicotine level of the test product was lower than those of general nicotine pouches on the European market. Further assessment of the acute health effects with the higher nicotine contents of nicotine pouches would be necessary to evaluate the potential impacts of Nordic Spirit on combustible cigarette smokers, who are the largest proportion of tobacco product consumers.
Secondly, clinical study results from different brands of nicotine pouches cannot necessarily be comparable, since a variety of nicotine pouch brands on the market have distinct formulations in terms of the source of nicotine and the other ingredients and formulation regarding fillers, pH adjusters, pouch materials etc. All these factors can affect nicotine absorption through the oral mucosa (the inside of the mouth) and/or the efficiency of nicotine extraction from the pouches, which impacts nicotine delivery. This would justify performing a clinical study dedicated to a specific nicotine pouch brand, to accurately evaluate its potential impact on the human body. Collecting this information could inform consumers' choice of their products and help regulators to develop science-based regulatory frameworks for nicotine pouches.
In summary, considering the new features of Nordic Spirit and limited safety information on the human use of tobacco-free oral nicotine pouches in the adult smoker population, the aim of this study is to measure the pharmacokinetic (PK) profile (i.e. what the body does to the nicotine) and the safety profile of Nordic Spirit in such a population, in terms of the nicotine exposure, time profiles of nicotine exposure and acute effects relevant to nicotine after the use of Nordic Spirit products.

Who can participate?
Healthy men and women aged 19-64 years who currently smoke combustible cigarettes and have done for at least 1 year.

What does the study involve?
Participants are randomly allocated to use nicotine products in one of ten sequences, including three Nordic Spirit products, combustible cigarettes and nicotine gum. Participants use each of the products once. The study assesses nicotine PK profiles and the acute effects of nicotine including changes in blood pressure and pulse rate, subjective effects following nicotine or tobacco product use and any adverse events. The amount of nicotine extracted from Nordic Spirit products following use will be also measured to assess the relationship between PK parameters and the extracted amount of nicotine.
Eligibility to participate in the study will be checked at the Screening. Participants will arrive at the clinical site on Day -1 and stay overnight until the end of the procedures of Day 5. On each day (Day 1 – Day 5), the following procedures will be performed: single investigational product use and blood sampling for nicotine PK, safety assessments, changes in vital signs, collection of used pouches of Nordic Spirit (for nicotine extraction analysis) and subject self-assessment of product experience. Participants shall be abstinent from cigarettes and all other nicotine-containing products for at least 12 hours before the start of each product use. The participants' safety and compliance with the study protocol will be carefully monitored by clinical staff throughout the whole stay at the clinical site. A follow-up telephone call (end-of-study) will be made 6-8 days after Day 5 or after early withdrawal to follow-up participants' safety.

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 established combustible cigarette smokers for at least 1 year so that they are well acquainted with and used to the effects and risks of nicotine. As such, participants will not be exposed to any increased health risks compared to their daily use of combustible cigarettes. The potential adverse effects from using the study products, which are commercially available, are likely to be minor and similar to the 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 such as 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?
MTZ Clinical Research (Poland)

When is the study starting and how long is it expected to run for?
July 2021 to October 2022

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

Who is the main contact?
Karine Renard
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# Contact information

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Public

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# Additional identifiers

### EudraCT/CTIS number
Nil known

### IRAS number

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
JTIG-2101-PL

# Study information

### Scientific Title
A randomized, open-label, crossover study to characterize nicotine pharmacokinetic parameters following use of novel nicotine-containing products for oral use compared to combustible cigarettes and nicotine gum in healthy adult smokers

### Study objectives
To characterize nicotine pharmacokinetic parameters following use of three variants of novel nicotine-containing products for oral use, compared to combustible cigarettes and nicotine gum.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approved 30/12/2021, Komisja Bioetyczna, przy Okręgowej Izbie Lekarskiej w Warszawie (Bioethics Committee, District Medical Board in Warsaw, Pulawska Street 18, 02-512 Warsaw, Poland; +48 (0)22 54 28 312; email: not available), ref: KB/1366/21

### 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)
Pharmaceutical testing facility

## 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 randomised to one of ten randomisation sequences according to a balanced Latin square (Williams) design 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 12 mg nicotine/pouch

Comparator products:
4. Combustible cigarettes (subject’s own brand)
5. Nicotine gum (Nicorette®, mint flavor gum) containing 4 mg nicotine/piece

For the Nordic Spirit, subjects will be asked to place a pouch between the upper lip and gum and keep it there for 30 minutes. For combustible cigarettes, subjects will smoke a cigarette for up to 5 minutes as maximum (smoking regimen is ad libitum). 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 analyzed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method for pharmacokinetic parameters using blood samples collected at pre-use (within 15 minutes before the start of investigational product use), 2 (only for combustible cigarettes), 5, 8, 10, 15, 20, 30, 45 minutes, and 1, 1.5, 2, 3, 4, 6 and 8 hours relative to the start of investigational product use

### Secondary outcome measures
1. Vital signs (blood pressure and pulse rate) measured using a sphygmomanometer and a pulse oximeter at baseline, 5, 30 and 60 minutes after the start of investigational product use
2. Subjective effects 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 measured using the Intent to Use the Product Again Questionnaire (visual analogue scale) following a single use of investigational products
4. Amount of nicotine released from Nordic Spirit products 6 mg, 9 mg and 12 mg measured using a validated ultra performance liquid chromatography (UPLC)-UV method 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 released amount of nicotine

### Overall study start date
30/07/2021

### Completion date
17/10/2022

## 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 smokes factory-made combustible cigarettes (the ISO tar yield ≥6 mg), who typically smokes at least 10 and a maximum of 30 cigarettes per day, who daily smokes the cigarettes (more than 5 days per week), and who has been smoking cigarettes for at least 1 year prior to the Screening
5. Positive urine cotinine test (>200 ng/ml) at Screening
6. Clinically normal medical history, physical findings, vital signs, ECG, low dose of computed tomography of lungs and laboratory values at the time of Screening, as judged by the Investigator
7. Subjects who are healthy, as judged by the Investigator, based on all available assessments at Screening and PK assessment days (safety laboratory testing, spirometry [forced expiratory volume in 1 second {FEV1} s/forced vital capacity {FVC} >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8], vital signs, physical examination, 12-lead ECG, and medical history)
8. Subjects who are able to place a pouch of Nordic Spirit 9 mg between gum and lip, in a 30-minute period without discomfort (the subjects will be asked to try a pouch of Nordic Spirit 9 mg during Screening)
9. 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
10. Negative to the coronavirus infection (PCR test on Screening, and antigen test on the day of check-in to the study site)

## 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, a medical/surgical procedure or trauma within 2 weeks prior to the first day of PK assessment
3. Malignancy within the past 5 years except for in situ removal of basal cell carcinoma
4. Any surgery within 6 months of the Screening visit that could negatively impact 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 childhood excluded)
7. Clinically significant liver disease (including total bilirubin, alkaline phosphatase, LDH, AST or ALT) as judged by the Investigator Any positive result on Screening for serum hepatitis B surface antigen, hepatitis C virus antibodies and HIV
8. Positive screen for drugs of abuse or alcohol at Screening or on admission to the Site prior to any use of the investigational product
9. Systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg, at least 5 minutes in the seated position
10. Poor peripheral venous access, as judged by the Investigator
11. Female subjects who are pregnant or who are currently breastfeeding
12. History of alcohol abuse or excessive intake of alcohol, as judged by the Investigator
13. Presence or history of drug abuse and/or anabolic steroids, as judged by the Investigator
14. Subjects who have used any tobacco/nicotine-containing products (including electronic cigarettes and heat-not-burn tobacco products) or NRT medications, other than factory-made combustible cigarettes within 14 days of Screening
15. Subjects who, prior to enrolment, are planning to quit tobacco use during the study period or are postponing a quit attempt 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
16. Any use of prescription or over-the-counter bronchodilator medication (e.g., inhaled or oral β-adrenergic agonists, cholinolytics or theophylline) to treat a chronic condition within the 12 months prior to the first day of PK assessment
17. Any medication (prescription or over-the-counter [OTC]) within 14 days or within five half-lives of the drug (whichever was longer) prior to the first day of PK assessment, which has an

impact on CYP2A6 activity
18. Plasma donation within one month of Screening or blood donation (or corresponding blood loss – 450 ml) during the 3 months prior to Screening
19. Planned treatment or treatment with another investigational product within 3 months prior to the first day of PK assessment. Subjects consented and screened but not dosed in previous phase I studies are not excluded
20. Subjects who are employed by the tobacco industry, the clinical site, or handle unprocessed tobacco as part of their job
21. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements

### Date of first enrolment
25/04/2022

### Date of final enrolment
01/06/2022

## Locations

### Countries of recruitment
Poland

### Study participating centre
**MTZ Clinical Research**
Pawinskiego 5, Str.
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## Sponsor information

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JT International SA

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### Sponsor type
Industry

### Website

https://www.jti.com

# Funder(s)

**Funder type**
Industry

**Funder Name**
JT International SA

# Results and Publications

**Publication and dissemination plan**
It is planned to publish the data at a scientific conference or in a peer reviewed journal after the clinical study report is finalized

**Intention to publish date**
20/12/2024

**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