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A study to investigate the delivery of nicotine in the bloodstream from seven variants of tobacco-free oral nicotine pouches (Modern oral products), for comparison to a commercial snus product

Submission date	**Recruitment status**	[_] Prospectively registered
10/12/2019	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
27/05/2020	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
08/06/2020	Other	[_] Record updated in last year

Plain English summary of protocol

Background and study aims

Cigarette smoking is a leading cause of numerous human disorders including lung cancer, pulmonary disease and cardiovascular disease. Cigarette smoke is a complex and dynamic mixture of more than 6,500 identified chemical constituents, some of which have been identified as potential contributors to the disease-causing effects of cigarette smoke.

Recently, oral nicotine products containing little or no tobacco (henceforth referred to as 'modern oral') have emerged on the market as potential alternatives to existing oral tobacco products. One such product is "Lyft" (also known as "VELO" in certain markets), a smokeless, tobacco-free oral product which is white in colour and comes in pouches containing high-quality food-grade ingredients including naturally derived nicotine, water, cellulose, flavourings and sweeteners. Consumers place the pouch between their gum and upper lip, typically for up to 60 minutes. During use, nicotine and flavours are released and the nicotine is absorbed through the oral mucosa in the gum.

Research conducted by the sponsor suggests that Lyft modern oral products have a lower toxicant profile and reduced biological response compared to traditional tobacco-containing snus products. Therefore, understanding the rate of nicotine uptake is key information required to further characterise these products as potential alternatives to cigarette smoking and traditional snus use.

The aim of this study is to investigate the delivery and levels of nicotine in the bloodstream from seven variants of modern oral products and a snus product. From this, the researchers aim to obtain data to understand product efficacy at delivering nicotine, provide safety data, and to inform product design.

Who can participate?

Healthy adults aged 19-55 who are current daily users of snus or modern oral products

What does the study involve?
Participants will attend a screening visit to assess eligibility to participate in the study. Once deemed eligible, they will be admitted into the clinic (day -1) within 28 days of the screening visit, in which they will remain in the clinic for 8 days until discharge (day 8). During the participants stay at the clinic, they will be allowed to familiarise with the study products before their assessment. During the assessment period, they will use their assigned products for a maximum of 60 minutes. Before, during and up to 6 hours after product use, blood samples will be collected for nicotine analysis. A product satisfaction questionnaire and an overall intent to use again questionnaire will be completed at predefined intervals during this 6-hour period. The same procedure will be repeated on each study day until all the study products are used.

What are the possible benefits and risks of participating?
The possible benefit to participants taking part in this study is that the tests involved may help them learn about their general health or discover any unknown medical conditions. As participants already use tobacco products (snus or modern oral products), only the standard risks and side effects associated with nicotine and tobacco use apply. During study product use, it is not expected that subjects would be exposed to nicotine levels higher than those they are usually exposed to during their daily consumption of nicotine and tobacco products. The possible side effects of modern oral use include headache, dizziness, nausea, palpitations, mouth and throat irritation, skin irritation and gastrointestinal disturbances. Participants will be monitored for any of the listed symptoms.

Where is the study run from?
IRW Consulting (Sweden)

When is the study starting and how long is it expected to run for?
October 2019 to November 2020

Who is funding the study?
British American Tobacco (UK)

Who is the main contact?
David Azzopardi
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
BAT2119018

Study information

Scientific Title
A multi-centre, randomised, cross-over, pharmacokinetic study of 8 oral nicotine products

Study objectives
To determine the kinetics of nicotine absorption into the blood of subjects using different variants of smokeless nicotine products and to compare the nicotine PK parameters between smokeless nicotine products.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/03/2020, Central Swedish Ethics Committee (Etikprövningsmyndigheten, Box 2110, 750 02 Uppsala, Sweden; +46 (0)10 475 08 00; registrator@etikprovning.se), ref: 2019-06341

Study design
Multi-centre randomised pharmacokinetic cross-over study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

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
The following products will be administered in the study as 60-minute single product administrations:
1. Swedish Snus (pouch) – Granit Vit Stark with 13 mg/pouch nicotine
2. Lyft (commercial product), 4 mg/pouch
3. Lyft (commercial product), 10 mg/pouch
4. Lyft non-commercial (alginate removed), 10 mg/pouch
5. Lyft non-commercial (benzoic acid added), 4 mg/pouch
6. Lyft non-commercial (benzoic acid added), 10 mg/pouch
7. Lyft non-commercial (citric acid added), 10 mg/pouch
8. Lyft non-commercial (benzoic acid added, sweet base), 10 mg/pouch

Intervention Type
Other

Primary outcome measure
Plasma nicotine levels analysed for the following parameters using blood samples pre-dose (up to 5 minutes before the product use), and then at 5, 10, 20, 40, 60, 65, 75, 90, 120, 240 and 360 minutes following the start of administration:
1. Cmax
2. AUC0-6h

Secondary outcome measures
1. Product liking assessment, assessed using the Subjective Product Liking Questionnaire (PLQ) following product use
2. Intent to use product again, assessed using the Overall Intent to Use Again (OIUA)

questionnaire following product use
3. Mouth Levels Exposure (MLE), assessed by measuring nicotine levels in pouches after use in PK session for comparison to unused products

Overall study start date
21/10/2019

Completion date
30/11/2020

Eligibility

Key inclusion criteria
Healthy daily user of smokeless snus or modern oral nicotine products aged 19-55 years

Participant type(s)
Healthy volunteer

Age group
Adult

Sex
Both

Target number of participants
36

Total final enrolment
36

Key exclusion criteria
1. Female who is lactating at screening
2. Female who is pregnant according to the pregnancy test at screening or prior to the first study product administration
3. Presence of braces, partials, dentures or any dental work that could, in the opinion of an investigator, affect the conduct of the study (including missing molars)
4. Presence or history of significant form of oral and/or pharyngeal inflammation, oral lesions and/or gum disease or temporomandibular joint dysfunction
5. History of significant hypersensitivity to any excipients of the formulations as well as severe hypersensitivity reactions (like angioedema) to any drugs
6. Presence or history of significant gastrointestinal, liver or kidney disease, or surgery that may affect nicotine bioavailability
7. History of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease
8. Presence of clinically significant ECG abnormalities at the screening visit, as defined by medical judgment
9. Maintenance therapy with any drug (with the exception of hormonal contraceptives or hormone replacement therapy) or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic)
10. Any clinically significant illness in the 28 days prior to the first study product administration

11. Use of any prescription drugs (with the exception of hormonal contraceptives or hormone replacement therapy) in the 28 days prior to the first study product administration, that in the opinion of an investigator would put into question the status of the participant as healthy
12. Use of any medication or substance that aids in smoking cessation, including but not limited to any nicotine replacement therapy (e.g., nicotine gum, lozenge, patch), varenicline (Champix®), bupropion (Wellbutrin®, Zyban®), or Lobelia extract in the 28 days prior to the first study product administration
13. Any history of tuberculosis
14. Positive test result for alcohol and/or drugs of abuse at screening or prior to the first product administration
15. Positive screening results to HIV Ag/Ab Combo, Hepatitis B surface Antigen (HBsAG (B) (hepatitis B)) or Hepatitis C Virus (HCV (C)) tests
16. Previous inclusion in this clinical study
17. Intake of an Investigational Product (IP) in any other clinical study in the 28 days prior to the first study product administration
18. Subjects who have donated:
18.1. ≥400 mL of blood within 90 days prior to admission
18.2. Plasma in the 7 days prior to admission
18.3. Platelets in the 6 weeks prior to administration
19. Postponement of a decision to quit using tobacco- or nicotine-containing products in order to participate in this study
20. Previously attempted to quit using tobacco- or nicotine-containing products in the 28 days prior to the first study product administration
21. Employees or immediate relatives of the tobacco industry or the clinical site

Date of first enrolment
15/01/2020

Date of final enrolment
06/03/2020

Locations

Countries of recruitment
Sweden

Study participating centre
The Karolinska Trial Alliance (KTA) Phase I Unit
Karolinska Universitetssjukhuset Huddinge, Avdelning M62
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Study participating centre
The Skåne University Hospital, Clinical Studies Sweden – Forum South, Clinical Trial Unit
R&D Centre, Skane University Hospital, Skane
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Organisation
British American Tobacco (Investments)

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
British American Tobacco

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
To publish data once CSR is finalised

Intention to publish date
31/10/2020

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 V3.0	06/04/2020	08/06/2020	No	No