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A study to investigate the delivery of nicotine in the bloodstream from three variants of tobacco-free oral pouches (modern oral products), for comparison to four commercial products and a conventional cigarette

Submission date
10/12/2019

Recruitment status
No longer recruiting

Registration date
02/04/2020

Overall study status
Completed

Last Edited
20/12/2021

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Cigarette smoking is a leading cause of numerous human disorders including lung cancer, lung disease and heart 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", 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, eucalyptus and pine tree fibres, flavouring 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.
Chemical analysis and in vitro data conducted by the sponsor suggests that Lyft modern oral products demonstrate 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 three variants of modern oral developed by British American Tobacco, in comparison to four competitor modern oral products as well as a conventional cigarette.

Who can participate?
Healthy adults aged 19-55 who are current daily users of snus or modern oral products and occasional smokers of conventional factory-made cigarettes.

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 subjects stay at the clinic, they will be allowed to familiarise with the study products before their assessment. During the assessment period, participants will use their assigned products for a maximum of 60 minutes for modern oral products and 5 minutes for the combustible cigarette. Before, during and up to 6 hours after product use, blood samples will be collected for nicotine analysis. Participants complete a product satisfaction questionnaire and an overall intent to use again questionnaire 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, modern oral products and cigarettes), only the standard risks and side effects associated with nicotine and tobacco use apply. During study product use, it is not expected that participants 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?
A + Science (Sweden)

When is the study starting and how long is it expected to run for?
October 2019 to May 2020 (updated 27/05/2020, previously: August 2020)

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

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
BAT2119019

Study information

Scientific Title
A single-dose, randomised, crossover study to assess the pharmacokinetics of oral nicotine products and a cigarette in healthy adults who smoke combustible cigarettes and use smokeless pouch products

Study objectives
To determine the pharmacokinetics (PK) of nicotine absorption into the blood of subjects using different variants of smokeless nicotine products (pouches) as well as a combustible cigarette.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/03/2020, Central Swedish Ethics Committee (Etikprövningsmyndigheten, Box 2210, 750 02 Uppsala, Sweden; +46 (0)10 475 08 00; registrator@etikprovning.se), ref: 2019-06294

Primary study design
Interventional

Study design
Single-dose randomised open-label crossover pharmacokinetic study

Study type(s)
Other

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

Interventions
Subjects will attend the clinic site for a pre-study screening visit within 28 days of entry into the study. Subjects who satisfy the inclusion/exclusion criteria will enter the study. Subjects will attend the clinical site approximately 8,5 days during the study for pharmacokinetic measurements and other study procedures. Eight (8) study products will be administered to each subject (one per day). Prior to each product administration, subjects will be required to refrain from using nicotine products for a period of at least 12 hours. Subjects will use pouch products for a fixed period of 60 minutes and a combustible cigarette for a maximum of 5 minutes, during and after which blood samples will be obtained for plasma nicotine analysis. Blood samples will be taken within 5 minutes prior to the start of study product administration and at 3, 5, 7, 10, 20, 45, 60, 65, 75, 120, 240, and 360 minutes following the start of administration. For the pouch products, questionnaires of product subjective measures will be administered after each PK session. The blood samples, the used pouches and the used cigarette filters will be sent to a bioanalysis laboratory for nicotine analysis.

The study products will be:
1. Pall Mall Red Cigarette (0.66 mg ISO nicotine)
2. Modified Lyft 20 mg/pouch nicotine
3. Modified Lyft 10 mg/pouch nicotine
4. Commercial Lyft 10 mg/pouch nicotine (Scandinavian style)
5. Zyn (Wet) Spearmint 10 mg/pouch nicotine
6. Nordic Spirit Mint 9 mg/pouch nicotine
7. On! Mint 6 mg/pouch nicotine
8. Skruf super white fresh stark #3 8 mg/pouch nicotine

Intervention Type
Other

Primary outcome(s)
Plasma nicotine levels will be analysed for the following parameters using blood samples 5 minutes before the product use, and then at 3, 5, 7, 10, 20, 45, 60, 65, 75, 120, 240 and 360 minutes following the start of administration:
1. Cmax
2. Tmax
3. AUC0-360

Key secondary outcome(s)
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 cigarette filters after use and in pouches after use in PK session for comparison to unused products

Completion date
19/05/2020

Eligibility

Key inclusion criteria

1. Provision of signed and dated informed consent form (ICF)
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Healthy adult male or female
4. If female, meets one of the following criteria:
4.1. Is of childbearing potential and agrees to use two of the accepted contraceptive regimens from at least 28 days prior to the first study product administration through to at least 30 days after the last dose of study product. An acceptable method of contraception includes one of the following:
4.2. Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
4.3. Intrauterine device (with or without hormones)
4.4. Barrier methods of contraception (male condom with spermicide, female condom, cervical cap, diaphragm, contraceptive sponge)
4.5. Male partner vasectomised at least 6 months prior to the first study product administration
Or
4.6. Is of childbearing potential and agrees to abide by true abstinence from heterosexual intercourse, when this is in line with the preferred and usual lifestyle (not periodic abstinence)
Or
4.7. Male partner has had a vasectomy less than 6 months prior to dosing, and agrees to use an additional acceptable contraceptive method from the first study product administration through to at least 30 days after the last dose of study product
Or
4.8. Is of non-childbearing potential, defined as surgically sterile (i.e. has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or is in a postmenopausal state (i.e. at least 1 year without menses without an alternative medical condition prior to the first study product administration)
5. Aged at least 19 years but not older than 55 years
6. Body mass index (BMI) within 18.5 kg/m2 to 30.0 kg/m2, inclusively
7. Minimal body weight of 52 kg (males) or 45 kg (females)
8. Daily snus user and have used snus products for at least 6 months and who use snus products under their upper lip. Subjects who use pouched snus should regularly use pouch weights of 0.8 g and above, and at least 8 mg nicotine/pouch.
9. Subject must be able to use 3 or more 8 mg nicotine pouches in a 3 hour period without any discomfort
10. Smoker of 5 cigarettes or more on average per week and who has smoked for at least 1 year prior to the first study product administration
11. Stated willingness to abstain from nicotine and tobacco products (except for the study products provided) from 12 hours prior to each study product administration until the end of each PK sampling
12. Positive urine cotinine test (≥50 ng/mL) at screening and prior to the first study product administration
13. Successful completion of the product familiarisation session for study product use prior to the first study product administration (subject is able to follow the instructions and does not experience AEs during the training session)
14. Clinical laboratory values within the laboratory's stated normal range; if not within this range, they must be without clinical significance, as determined by an investigator
15. Have no clinically significant diseases captured in the medical history or evidence of clinically significant findings on the physical examination (including oral mucosa examination and vital signs) and/or electrocardiogram (ECG), as determined by an investigator

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
35

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. Self-reported non-inhalers of cigarettes (smokers who draw the smoke from the cigarette into the mouth and throat but who do not inhale)
4. 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)
5. Presence or history of significant form of oral and/or pharyngeal inflammation, oral lesions and/or gum disease or temporomandibular joint dysfunction
6. History of significant hypersensitivity to any excipients of the formulations as well as severe hypersensitivity reactions (like angioedema) to any drugs
7. Presence or history of significant gastrointestinal, liver or kidney disease, or surgery that may affect drug bioavailability
8. History of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease
9. Presence of clinically significant ECG abnormalities at the screening visit, as defined by medical judgment
10. 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)
11. Any clinically significant illness in the 28 days prior to the first study product administration
12. 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
13. 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 (Chantix®), bupropion (Wellbutrin®, Zyban®), or Lobelia extract in the 28 days prior to the first study product administration
14. Any history of tuberculosis
15. Positive test result for alcohol and/or drugs of abuse at screening or prior to the first product administration

16. Positive screening results to Hepatitis B surface antigen (HbsAG), hepatitis C antibody or HIV
17. Previous inclusion in this clinical study
18. Intake of an Investigational Product (IP) in any other clinical trial in the 28 days prior to the first study product administration
19. Subjects who have donated:
19.1. ≥400 mL of blood within 90 days prior to admission
19.2. Plasma in the 7 days prior to admission
19.3. Platelets in the 6 weeks prior to administration
20. Postponement of a decision to quit using tobacco- or nicotine-containing products in order to participate in this study
21. Previously attempted to quit using tobacco- or nicotine-containing products in the 28 days prior to the first study product administration.
22. Employees or immediate relatives of the tobacco industry or the clinical site.

Date of first enrolment
07/03/2020

Date of final enrolment
03/05/2020

Locations

Countries of recruitment
Sweden

Study participating centre
Clinical Trial Consultants AB
Dag Hammarskjolds vag 10B
Uppsala
Sweden
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Sponsor information

Organisation
British American Tobacco (United Kingdom)

ROR
https://ror.org/01znsh139

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

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		18/12/2021	20/12/2021	Yes	No