ISRCTN65708311 https://doi.org/10.1186/ISRCTN65708311

A study to assess the nicotine uptake of three oral nicotine products in healthy adult smokers

Submission date 17/03/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 18/03/2020	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 29/04/2022	**Condition category** Other	[_] Individual participant data

Plain English summary of protocol

Background and study aims
A wide range of nicotine delivery products have emerged in the marketplace to provide consumers with alternative to cigarette smoking, via inhalation (electronic cigarettes) and oral (snus) routes of nicotine administration. Adequate delivery of nicotine to the consumer from such products is critical to support them during their smoking cessation attempt. Where the safety and/or disease risk potential of these alternative products is not benign, and in the case of electronic cigarettes, not known, manufacturers nonetheless continually strive to develop safer products to support smokers who wish to quit smoking, but continue to use nicotine. Recently, a modern oral nicotine product, which does not contain tobacco, has emerged as a potential alternative to existing oral tobacco products. In order to determine the potential of this product to provide suitable levels of nicotine to maintain smoking cessation, this PK study seeks to characterise the product relative to existing methods of smoking cessation, such as nicotine gum and nicotine lozenges.

Who can participate?
Healthy adult smokers aged 19 - 55 years (updated 20/07/2020, previously: 21 – 55 years)

What does the study involve?
Eligible subjects will undergo a training session on how to correctly administer the different nicotine products within 36 to 24 hours prior to the first product administration. Following successful completion of the training session, subjects will be randomized to receive 1 of 6 treatment sequences, where each of the 3 different nicotine products will be administered in 3 sequential periods. In each study period, a product containing 4 mg of nicotine will be administered orally in the morning, following a minimum of an 8-hour overnight fast.

What are the possible benefits and risks of participating?
There will be no medical advantages as a result of using the study products. However, the subjects will undergo a medical examination, which may provide them with information on their state of health. Subjects will be able to ask for advice to stop using tobacco/nicotine products and will be provided with a smoking cessation helpline number. The results of the study will add

to the current knowledge of nicotine delivery from oral nicotine product (pouch). This may help manufacturers to design better products which may help people to stop smoking conventional cigarettes.

Where is the study run from?
Altasciences (Canada)

When is the study starting and how long is it expected to run for?
May 2020 to May 2021

Who is funding the study?
Imperial Tobacco Canada Ltd

Who is the main contact?
Dr James K. Ebajemito
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
BAT2219017

Study information

Scientific Title
Single dose, randomized, crossover study to assess the pharmacokinetics of three oral nicotine products in healthy adult smokers under fasting conditions

Study objectives
1. There will be comparable bioavailability of Test product versus the Reference products
2. The Test product will be bioequivalent to the Reference products

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/02/2020, Advarra Ethics Committee (372 Hollandview Trail, Suit 300, Aurora, Ontario L4G OA5, Canada; +1 905-727-7989; no email provided), ref: MOD00599289

Study design
Single center randomized single-dose laboratory-blinded 3-period 6-sequence crossover study

Primary study design
Interventional

Secondary study design
Randomised controlled 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
Oral nicotine use

Interventions
Test Product: Nicotine Pouch, 4 mg
Reference Product 1: Nicotine Gum, 4 mg
Reference Product 2: Nicotine Lozenge, 4 mg

Eligible subjects will undergo a training session on how to correctly administer the different nicotine products within 36 to 24 hours prior to the first product administration. Following successful completion of the training session, subjects will be randomized to receive 1 of 6 treatment sequences, where each of the 3 different nicotine products will be administered in 3 sequential periods. In each study period, a product containing 4 mg of nicotine will be administered orally in the morning, following a minimum of an 8-hour overnight fast.

For each treatment sequence, the product administrations will be separated by at least 24 hours (between the start of product administrations). PK blood samples will be collected up to 12 hours post dose for each period. PK blood samples will be collected at 0, 5, 10, 20, 30, 40, 50 min and 1, 1.25, 2, 3, 4, 5, 6, 8, 9, 10, 11, and 12 hours.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Nicotine

Primary outcome measure
Measured by PK blood samples will be collected at 0, 5, 10, 20, 30, 40, 50 min and 1, 1.25, 2, 3, 4, 5, 6, 8, 9, 10, 11, and 12 hours:
Cmax and AUC0-T of nicotine

Secondary outcome measures
Bioequivalence of Test product compared to Reference products within the 80.0 to 125.0% bioequivalence range measured as above.

Overall study start date
23/07/2019

Completion date
29/05/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 20/07/2020:

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:
-Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
-intrauterine device (with or without hormones)
-Barrier methods of contraception (male condom with spermicide, female condom, cervical cap, diaphragm, contraceptive sponge)
-Male partner vasectomized at least 6 months prior to the first study product administration
Or

4.2. 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
4.3. 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
4.4. 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 50 kg
8. Primary tobacco product used in the last 6 months is combustible cigarettes or roll-your-own cigarettes
9. A smoker of 10 cigarettes or more >6 mg ISO tar per day who has smoked for at least 6 months prior to the first study product administration
10. Stated willingness to abstain from nicotine and tobacco products (except for the study products provided) from 24 hours prior to the first study product administration until the end of the study
11. Positive urine cotinine test (≥200 ng/mL) at screening and prior to the first study product administration
12. Successful completion of the training session for study product use prior to the first study product administration (subject is able to follow the instructions and does not experience adverse events during the training session)
13. 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
14. 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 ECG, as determined by an investigator

Previous 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:
-Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
-intrauterine device (with or without hormones)
-Barrier methods of contraception (male condom with spermicide, female condom, cervical cap, diaphragm, contraceptive sponge)
-Male partner vasectomized at least 6 months prior to the first study product administration
Or
4.2. 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
4.3. 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
4.4. 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 21 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 50 kg
8. Primary tobacco product used in the last 6 months is combustible cigarettes or roll-your-own cigarettes
9. A smoker of 10 cigarettes or more >6 mg ISO tar per day who has smoked for at least 6 months prior to the first study product administration
10. Stated willingness to abstain from nicotine and tobacco products (except for the study products provided) from 24 hours prior to the first study product administration until the end of the study
11. Positive urine cotinine test (≥200 ng/mL) at screening and prior to the first study product administration
12. Successful completion of the training session for study product use prior to the first study product administration (subject is able to follow the instructions and does not experience adverse events during the training session)
13. 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
14. 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 ECG, as determined by an investigator

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Approximately 36 subjects will be randomized to complete with at least 30 subjects.

Total final enrolment
34

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 any tongue piercings or history of any tongue piercings in the last 90 days prior to the first study product administration
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 pseudoephedrine in the 7 days prior to the first study product administration
14. 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
15. Any history of tuberculosis
16. Positive test result for alcohol and/or drugs of abuse at screening or prior to the first product administration
17. Positive screening results to HIV Ag/Ab Combo, Hepatitis B surface Antigen (HBsAG (B) (hepatitis B)) or Hepatitis C Virus (HCV (C)) tests
18. Inclusion in a previous group for this clinical study
19. Intake of an Investigational Product (IP) in any other clinical trial in the 28 days prior to the first study product administration
20. Donation of 50 mL or more of blood in the 28 days prior to the first study product administration
21. Donation of 500 mL or more of blood (Canadian Blood Services, Hema-Quebec, clinical studies, etc.) in the 56 days prior to the first study product administration
22. Postponement of a decision to quit using tobacco- or nicotine-containing products in order to participate in this study
23. Previously attempted to quit using tobacco- or nicotine-containing products in the 28 days prior to the first study product administration

Date of first enrolment
20/07/2020

Date of final enrolment
11/08/2020

Locations

Countries of recruitment
Canada

Study participating centre
Altasciences
1200 Beaumont Ave.
Mount-Royal
Montreal
Canada
H3P 3P1

Sponsor information

Organisation
British American Tobacco (United Kingdom)

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Sponsor type
Industry

Website
https://www.bat-science.com/

ROR
https://ror.org/01znsh139

Funder(s)

Funder type
Industry

Funder Name
Imperial Tobacco Canada Ltd

Results and Publications

Publication and dissemination plan
Full study protocol, statistical analysis plan, informed consent form, clinical study report will be available. Results from this study will be published in peer-reviewed scientific journals.

Intention to publish date
11/12/2021

Individual participant data (IPD) sharing plan
Deidentified participant level data will be available on request. This includes all data captured using the eCRF, questionnaires and full bioanalytical reports available in SDTM format for at least 5 years. This data will be available immediately following publication. Data will be available to anyone who wishes access to the data and for any purpose. Requests for data should be made to clinical_info@bat.com and data requestors must sign a data access agreement

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		28/04/2022	29/04/2022	Yes	No