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A study to assess nicotine pharmacokinetics for heated tobacco products and cigarettes

Submission date
08/04/2024

Recruitment status
No longer recruiting

Registration date
21/05/2024

Overall study status
Completed

Last Edited
30/06/2025

Condition category
Other

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

Plain English summary of protocol

Background and Study Aims
The purpose of this study is to evaluate the levels of nicotine in the blood following the use of three different tobacco products; the Ploom X Advanced heated tobacco device and associated tobacco sticks (two different flavours – Evo Gold and Evo Tan) and a conventional combustible cigarette (own brand). The main objectives are to measure nicotine levels in the blood following a single use of the three products; and assess different subjective measures i.e., completion of specific questionnaires around product usage such as intent to use, urge to smoke and product satisfaction after a single use and a 4-hour ad libitum use session; assess overall product consumption i.e., number of cigarettes smoked/tobacco sticks used over a 4-hour ad libitum use session; and, to provide general safety information for each of the three products.

Who can participate?
Healthy volunteers aged between 19 and 65 years old who are regular users of combustible factory-made conventional cigarettes with at least 12 months of consistent use and a daily user of an average of at least 10 cigarettes per day for the past 12 months who are not intending to quit or alter their nicotine usage during the study.

What does the study involve?
This study involves a screening visit (up to 28 days before the planned first product use), 3 product use assessment days (during a residential period requiring 4 overnight stays at the clinical unit from Day -1 to Day 4) and a post-study follow up telephone call (approximately 4-7 days after discharge from the clinical unit).

In this study, participants will be required to use two different flavours of Ploom X heated tobacco sticks (using the Ploom X Advanced heated tobacco device) and their cigarettes which they usually smoke daily, all of which are commercially available products in the UK. The study will comprise three product use periods; each period evaluating one of the products described across three study days. During each product use period, participants will be asked to complete two use sessions per day, one session where participants will use the product they have been assigned to on that day for a period of 4.5 minutes (10 puffs at 30-second intervals) and a second use session where participants will be required to use the product as they feel necessary for a period of up to 4 hours. During the single-use session each day, blood samples will be taken to

measure the levels of nicotine in the blood. In addition, participants will be asked to complete a series of questionnaires to assess different measures such as product satisfaction, the urge to smoke and the intent to use the products again.

What are the possible benefits and risks of participating?
Taking part in this study will not provide any medical benefit as the products are not designed or intended to be used as medicines or to aid in any attempt to quit smoking.

Possible risks include the following:
Blood sampling: A total of approximately 104 mL of blood will be taken. Blood sampling may cause discomfort, bruising, bleeding and/or soreness at or around the area of the needle insertion site. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain.

Blood pressure and pulse rate: The participant's blood pressure and pulse will be measured using an inflatable cuff which will be placed on the arm. They may experience mild discomfort in the arm whilst the cuff is inflated.

ECG: Small sticky pads will be placed on the participants' upper bodies before the ECG and an ECG machine will measure the electrical activity of the participant's heart. Before the pads are applied, the skin needs to be cleaned. Trained staff may need to shave/clip small patches of the participant's hair in these areas. Like Elastoplast® these sticky pads may be uncomfortable to remove.

Spirometry: Performing the lung function tests may cause some coughing, shortness of breath and lightheadedness.

COVID-19: Participants should also be aware of the risks of exposure to COVID-19. When participants attend the clinical unit at each visit, they may be asked to complete a self-declaration form and temperature check to confirm that they are not showing any early signs of COVID-19 infection and that they have not had any contact with individuals who are currently self-isolating or have tested positive (dependent on risk mitigation measures employed at the clinical unit at the time of clinical conduct).

Participants may also be required to have a negative COVID-19 test before admission to the clinical unit for any overnight stays as defined within the study protocol. This procedure may cause some mild discomfort in the nose or throat when the swab is being taken but this should resolve after the procedure has been completed.

Additionally, at the clinical unit, participants may be asked to wear a facemask during procedures where clinical staff cannot maintain a 2 m distance. It is noted that if participants have a medical exemption from wearing a face mask, they will not be required to do so. In any circumstance, to prevent risk of transmission between staff and participants, all staff will be wearing appropriate personal protective equipment i.e., face masks, face shields etc during the study.

Contraception: For male participants with a female partner of childbearing potential, they must agree to use an effective form of contraception from the time of signing the consent form until completion of the post-study follow-up telephone call.

Female participants of childbearing potential must agree to use two effective forms of contraception from the time of signing the consent form until 1 month following the last product use session on Day 3.

For males who have been sterilised or engage in non-vaginal intercourse, they will be required to use a condom to prevent exposure of semen to any partner (male or female) from the time of signing the consent form until completion of the post-study follow-up telephone call. If their partner is already pregnant or currently breastfeeding, they will be required to still use a condom from the time of signing the consent form until completion of the post-study follow-up telephone call. In addition, all male participants should not donate sperm from the Day 1 visit until the completion of the post-study follow-up telephone call.

Where is the study run from?
The study will be conducted at Simbec-Orion Clinical Pharmacology Unit, an MHRA Phase 1 accredited CRO based in South Wales.

When is the study starting and how long is it expected to run for?
December 2023 to June 2024

Who is funding the study?
This exploratory study is funded and sponsored by a tobacco company called JT International (SA), based and headquartered in Geneva, Switzerland.

Who is the main contact?
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Additional identifiers

Integrated Research Application System (IRAS)
339200

Protocol serial number
JTIG-2301-GB

Study information

Scientific Title
A single-centre, open-label, randomised, crossover study to assess the nicotine pharmacokinetics following use of heated tobacco products and combustible cigarettes

Study objectives
The primary objective of this study is:
1. To characterise nicotine pharmacokinetic (PK) parameters following single use (fixed regimen products – 4.5 minutes) of two heated tobacco products and use of participants' own brand ready-made combustible cigarette.

The secondary objectives of this study are:
1. To characterise participant subjective effects following single use and multiple ad libitum use of two heated tobacco products and combustible cigarettes.
2. To assess changes in heart rate and blood pressure following the use of study products.
3. To document product consumption during multiple ad libitum use (approximately 4 hours) of study products.
4. To document adverse events.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 22/02/2024, Wales Research Ethics Committee 2 (Wales Research Ethics Committee 2, Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)2922 941119; Wales.REC2@wales.nhs.uk), ref: 24/WA/0035

Primary study design
Interventional

Study design
Single-centre open-label randomized 3-period 6-sequence crossover study

Study type(s)
Other

Health condition(s) or problem(s) studied

Alternative consumer products for primary users of factory-made combustible cigarettes +/- other non-medicinal nicotine delivery products

Interventions

This is a single-centre, open-label, randomised, 3-period, 6-sequence crossover study to assess the nicotine pharmacokinetics following the use of heated tobacco products and combustible cigarettes. Participants will take part in 3 assessment days over 4 confinement days, such that each participant will receive 1 study product each day according to the sequence determined by the randomisation. Participants will be randomly allocated one of the product sequences according to a randomisation code produced by Simbec-Orion using the PROC PLAN procedure of SAS® (the most up-to-date version will be used and this will be documented in the Statistical Analysis Plan (SAP)). Participants will be numbered sequentially from 001 (i.e., 001, 002 etc.). Replacement participants will be assigned the same number as the participant they are replacing, however, 100 will be added to the number (i.e., 101 would replace 001 etc.).

Visit 1: Screening (Day -28 to Day -2):
• A government-issued identification (ID) containing an image of the participant will be used to confirm the participant's identification. If acceptable, the participant will be issued a Simbec Orion photographic ID that will be used for identification throughout the trial.
• After being given enough time to review and ask questions (if any) to the Investigator or designee, participants will be asked to sign the Informed Consent Document.
• Demographic data including year of birth, age, gender, race and ethnicity will be recorded.
• Medical/surgical/social history (e.g., alcohol, smoking) and prior/concomitant medication use will be completed for each participant).
• Smoking/Vaping history questionnaire (including the history of tobacco and nicotine-containing products use) will be completed for each participant.
• Vital signs (BP, heart rate (HR), and oral temperature) will be measured.
• Height and weight will be measured, and BMI will be calculated.
• A physical examination will be performed.
• An electrocardiogram will be recorded.
• A urine sample will be collected for urinalysis.
• A urine sample will be collected for drug abuse, cotinine screen and alcohol test. Participants with a positive result for drug abuse and alcohol test will be excluded.
• Blood samples will be collected for laboratory safety assessments.
• A serum pregnancy test will be performed (for all females). Participants with a positive result will be excluded.
• Participants will undergo spirometry to demonstrate forced expiratory volume in 1 second {FEV1} s/forced vital capacity {FVC} ≥0.7 at pre-bronchodilator and post-bronchodilator basal spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8.
• The participants will be evaluated for study inclusion, exclusion and restriction criteria.
• Adverse events and concomitant medications will be recorded.

Visit 2: Check-in (Day -1):
The following procedures will be conducted at Check-in:
• The Simbec Orion photographic ID that was issued at the screening visit will be used to confirm the participant's identification.
• Review inclusion/exclusion criteria (if inclusion and exclusion criteria are not met, the participant will be withdrawn from the study and replaced with another eligible participant).
• COVID-19 test.
• A urine sample will be collected for urinalysis.
• Blood samples will be collected for laboratory safety assessments.
• Serum pregnancy test for all females.

• A urine sample will be collected for drug abuse, cotinine screen and alcohol test. Participants with a positive result for drug abuse and alcohol test will be excluded.
• Medical, and social history (e.g., alcohol, smoking) will be reviewed and updated.
• Tobacco and nicotine-containing product use history will be reviewed for each participant.
• A brief (symptom-driven) physical examination will be performed.
• Vital signs (BP, HR and oral temperature).
• An electrocardiogram will be recorded.
• Adverse events and concomitant medications will be recorded.
• Participants will be trained on how to use the Ploom X device and associated tobacco sticks. Participants will demonstrate that they are able and willing to use the Ploom X device and associated tobacco sticks during the product training session.

Throughout the study confinement, standardised meals will be served. The participants will be restricted from using any tobacco and nicotine-containing products for 12 hours before the single ad libitum use of the assigned product on Day 1, Day 2 & Day 3.

Assessment Period (Day 1 to Day 3):
• On each assessment day, participants will be assigned 1 of the test products after at least 12 hours of abstinence from nicotine-containing product use.
• Participants will complete a single 4.5-minute use of the assigned test product (1 puff every 30 seconds and 10 puffs in total for Heated Tobacco Sticks or combustible cigarettes)
• The start time of the single 4.5-minute use of the product will be considered as 0 minutes and all subsequent timepoints will be calculated based on this timepoint.
• Blood samples will be collected to assess plasma nicotine PK at -5, 2, 5, 7, 10, 15, 30, 60, 120, and 240 minutes after the single 4.5-minute use period.
• Vital signs (HR and BP) will be measured within 10 minutes before the start of the single product use and 10, 30, 60, 120, 240 minutes and 8 hours after the single 4.5-minute use period.
• Subjective effects questionnaire: VAS – Urge to smoke will be collected within 5 minutes before the start of the product use.
• Subjective effects questionnaires: Response to VAS - Intent to Use the Product Again, VAS - Urge to smoke and mCEQ questionnaires will be collected at 15 minutes after the single use of the assigned product. Participants will be asked to complete the questionnaires after completion of other scheduled measurements (blood sampling).
• After the 4-hour single-use investigation period has ended, participants will start the multiple ad libitum use investigation period and they will use the assigned product ad libitum for a further 4 hours.
• Subjective effects questionnaires: Response to VAS, Intent to Use the Product Again and mCEQ questionnaires will be collected at the 8-hour timepoint during ad libitum use of the assigned product.
• The number of sticks or combustible cigarettes used will be recorded after each multiple ad libitum use period.
• Adverse events and concomitant medications will be recorded.

Check-out (Day 4):
The following procedures will be conducted during Check-out:
• Vital signs (BP, HR, and oral temperature).
• A brief (symptom-driven) physical examination will be performed.
• An ECG will be recorded.
• Blood samples will be collected for laboratory safety assessments.
• A urine sample will be collected for urinalysis.
• Adverse events and concomitant medications will be recorded.

In case of early termination, all procedures as per check-out will be performed.

Follow-up Telephone Call 4-7 days following Check out or Withdrawal:
A telephone call will be conducted by the study staff 4-7 days following Check-out (Day 4) or withdrawal to inquire about AEs and concomitant medication. Up to 2 documented attempts will be made to contact the participants.

The study end is defined as the last subject last visit. The study will take place in the Clinical Unit of Simbec-Orion Clinical Pharmacology (Clinical Unit) under full medical and nursing supervision. Simbec-Orion Clinical Pharmacology has on-site designated smoking rooms which are exempt from being smoke-free in accordance with Section 3 of The Smoke-free Premises (Wales) Regulations 2007.

Intervention Type
Other

Primary outcome(s)
The primary endpoints for this study are pharmacokinetic parameters derived from the analysis of plasma samples for the concentration of nicotine.

The parameters to be calculated are as follows:
1. Maximum observed plasma nicotine concentration (Cmax) following a single use.
2. Area under the plasma nicotine concentration versus time curve from time zero to 240 min post-start of a single use (AUC0-240) and to last observed non-zero concentration (AUC0-t).
3. Time of maximum observed plasma concentration (tmax) following a single use.

Assessment Days 1, 2 & 3: Blood samples will be taken at the following timepoints: pre-dose (5 min before the start of single use), 2, 5, 7, 10, 15, 30, 60, 120 and 240 minutes relative to the start of single use of the assigned product on each day.

Key secondary outcome(s)
The secondary outcome measures are as follows:

Subjective Effects Endpoints:
1. Response to the visual analogue scale (VAS) for Intent to Use the Product Again after single and multiple ad libitum product use.
2. Response to the visual analogue scale (VAS) for Urge to smoke before and after single product use.
3. Subscales of the modified Cigarette Evaluation Questionnaire (mCEQ, subscales: satisfaction; psychological rewards; aversion; enjoyment of respiratory tract sensations; and craving reduction) after single and multiple ad libitum use.

Physiological Endpoint:
Actual and change from baseline blood pressure (BP) and heart rate (HR) measurements up to 240 minutes following the start of single-use.

Safety Endpoints:
1. Physical examination
2. Vital signs (except physiological endpoints)
3. 12-lead electrocardiogram (ECG)
4. Clinical laboratory evaluations
5. AEs/ SAEs recording

Other Endpoint:
Number of sticks or cigarettes consumed during the multiple ad libitum session.

Secondary outcomes will be assessed through assessments at the following timepoints:
• Assessment Days 1-3 - Completion of Visual Analogue Scale (VAS) for Intent to Use the Product Again Questionnaires: 15 minutes after product use in the single 4.5-minute product use period and at the 8-hour timepoint during ad libitum use of assigned product on each day.

• Assessment Days 1-3 - Completion of Visual Analogue Scale (VAS) for Urge to Smoke Questionnaires: 5 minutes before the start of product use and 15 minutes after product use in the single 4.5-minute product use period on each day.

• Assessment Days 1-3 - Completion of modified Cigarette Evaluation Questionnaire (mCEQ): 15 minutes after product use in the single 4.5-minute product use period and at the 8-hour timepoint during ad libitum use of the assigned product on each day.

• Physical Examination: Screening, Day -1 and Day 4

• Vital Signs (Complete): Screening, Day -1 and Day 4

• Vital Signs (Blood Pressure & Heart Rate) Assessment Days 1-3: 10 minutes before the start of a single 4.5-minute product use period, and at 10, 30, 60, 120, 240 minutes and 8 hours relative to the start of a single 4.5-minute product use period on each day.

• 12 Lead ECG: Screening, Day -1 and Day 4

• Clinical Laboratory Evaluations: Screening, Day -1 and Day 4

• Adverse Events: collected from informed consent through to post-study telephone call

• Number of Sticks Consumed Assessment Days 1-3: throughout 4-hour ad libitum use period on each day

Completion date
11/06/2024

Eligibility

Key inclusion criteria
1. Male or female participants aged from 19 to 65 years inclusive at Screening Visit.
2. Participant lives in the UK.
3. Participant can read, understand and sign a Participant Information Sheet (PIS) and Informed Consent Form (ICF) and complete questionnaires written in English.
4. Participants with a negative COVID-19 test on Day -1.
5. Participant must be an established user of combustible cigarettes and report an average consumption of at least 10 manufactured combustible cigarettes per day for at least 12 months before the screening visit. Participants may use e-cigarettes or heated tobacco products in addition to combustible cigarettes, provided that combustible cigarettes are the participant's primary source of nicotine consumption.
6. Participant has positive urine cotinine tests (> 200 ng/mL) at Screening Visit and Check-in.

7. Participant is healthy, as judged by the Principal Investigator (PI), based on all available assessments at the Screening Visit and Check-in (e.g., safety laboratory measures, spirometry [forced expiratory volume in 1 second {FEV1} s/forced vital capacity {FVC} ≥ 0.7 at pre-bronchodilator and post-bronchodilator basal spirometry, post-bronchodilator FEV1 ≥ 80% predicted value, and post-bronchodilator FVC ≥ 0.8], vital signs, physical examination, 12-lead ECG, and medical history).
8. Participant is willing to comply with all investigation procedures.
9. Female participant of childbearing potential who must be willing to use 2 effective forms of contraception from the time of signing the ICF until 1 month following the last product use session on Day 3 or be surgically sterile for at least 3 months before the Screening Visit.
10. Male participant (and partner of childbearing potential) willing to use an effective form of contraception, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the participant) from the time of signing the ICF until completion of the post-study follow up telephone call.
11. Female participant of menopausal status confirmed by demonstrating at Screening that the serum level of the follicle-stimulating hormone (FSH) falls within the respective pathology reference range. In the event, that a participant's menopausal status has been clearly established (for example, the participant indicates she has been amenorrhoeic for 10 years, confirmed by medical history, etc), but serum FSH levels are not consistent with a postmenopausal status, determination of the participant's eligibility to be included in the study will be at the Investigator's discretion following consultation with the Sponsor.
12. Participant who, before enrolment, is not planning to quit/reduce their cigarette/nicotine usage in the next 8 weeks. All participants will be informed that they are free to quit nicotine use and withdraw from the study at any time.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
19 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
24

Key exclusion criteria
1. As per the Principal Investigator judgment, the participant cannot participate in the study for any reason (e.g., medical, psychiatric, poor peripheral venous access, and/or social reasons).
2. Participant is legally incompetent, physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners or participant who is involuntarily

incarcerated).
3. Participant has a medical condition that requires smoking cessation, or clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, haematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease, or any other medical condition [including but not limited to clinically relevant abnormal laboratory parameters]) in the judgment of the Principal Investigator.
4. As per the Principal Investigator judgment, the participant has medical conditions which require or in the course of the study would have required, a medical intervention (e.g., the start of treatment, surgery, hospitalisation) which could have interfered with the study participation and/or study results.
5. Participant has a body mass index (BMI) <18.5 kg/ m2 or BMI ≥32.0 kg/m2 at the Screening Visit.
6. Participant has an acute illness (e.g., upper respiratory tract infection, viral infection, etc) requiring treatment within 4 weeks before Screening or on admission.
7. Participant has received any treatment with smoking cessation medications (e.g., Bupropion, Chantix or any form of nicotine replacement therapy) within 4 weeks before Check-in.
8. Participant has received medication (prescription or over-the-counter [OTC]) within 14 days or within 5 half-lives of the drug before Check-in that induces or inhibits CYP2A6 activity.
9. Participant has a positive alcohol test and/or participant has a history of alcohol abuse that could interfere with participant's participation in study.
10. Participant has a positive urine drug test.
11. Participant has used an e-cigarette in which the e-liquid contains cannabis within 3 months before Check-in.
12. Participant has a positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B, or hepatitis C.
13. Donation of 450 mL or more blood within the 3 months before first product use.
14. Participant is a current or former employee of the tobacco or vaping industry or is a first-degree relative (parent, sibling, child).
15. Participation in a New Chemical Entity (NCE) clinical study within the previous 3 months or five half-lives, whichever is longer, or a marketed drug clinical study within 30 days or five half-lives, whichever is longer, before the first product use. (Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
16. Participant has previously participated in the same study at a different time (i.e., each participant can be included in the study population only once).
17. Female participant of childbearing potential who is pregnant or breastfeeding.

Date of first enrolment
26/03/2024

Date of final enrolment
20/05/2024

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec Research Limited
Simbec House Merthyr Tydfil Industrial Park
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Sponsor information

Organisation
JT International SA

Funder(s)

Funder type
Government

Funder Name
JT International SA

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 25/10/2024:
The datasets generated during and/or analysed during the current study are not expected to be made available due to reasons associated with commercial confidentiality and sensitivity.

Previous IPD sharing plan:
The study data may be shared with relevant research groups and external stakeholders collaborating with the study sponsor to support the future development of the product within the boundaries of strict confidentiality agreements.
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Basic results	version 1.0	26/06/2025	30/06/2025	No	No