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A study to understand and compare the concentration of nicotine in the blood in healthy male and female participants who are current daily users of any tobacco and/or non-medicinal electronic nicotine delivery products using a Logic compact device with associated e-liquid pods of similar nicotine concentration with and without nicotine salts

Submission date	Recruitment status	[_] Prospectively registered
04/05/2022	No longer recruiting	[_] Protocol
Registration date	Overall study status	[_] Statistical analysis plan
20/05/2022	Completed	[X] Results
Last Edited	Condition category	[_] Individual participant data
15/03/2023	Other	

Plain English summary of protocol

Background and study aims

E-cigarette products are considered alternative consumer products to conventional 'normal' cigarettes and are available in a number of different types of designs, pod systems and flavours. These products are commercially available but are not marketed as having any health benefits and are not licensed as a medication to help users to quit smoking; they are simply considered as another category of nicotine delivery products.

The aims of this study are:

1. To measure the levels of nicotine in the blood following single and multiple use of two different types of Logic Compact e-liquids (nicotine strength 18 mg/ml, one liquid with nicotine salts and one without nicotine salts), and to measure the differences between the two different types of the Logic Compact e-liquid by evaluating different subjective measures i.e., completion of specific questionnaires around product usage such as intent to use, product satisfaction etc.
2. To determine the amount of nicotine delivered into the body following single and multiple use sessions of both types of e-liquids (one containing nicotine salts and one without nicotine salts) and to assess if there are any variations in the amount of nicotine delivered, and to provide general safety information for the two types of Logic Compact e-liquids.
3. To provide general safety information for the two types of Logic Compact e-liquids.

The data from this study will be used to provide further information in relation to e-cigarette products, specifically the evaluation of the differences in the nicotine concentration in the blood between e-liquids containing nicotine salts and e-liquids without nicotine salts. In addition, the

data will provide information as to the overall user satisfaction for each product which will support the study sponsor in future product development. The data will not be used to support any kind of marketing or advertising claims in relation to the effectiveness of the use of e-cigarette products or the development of these products as aids to support any attempts to quit smoking.

Who can participate?
Men and women aged between 19 and 65 years of age who are current daily users of tobacco /non-medicinal nicotine-containing e-cigarette products 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), two product use assessment days (during a residential period requiring 3 overnight stays at the clinical unit from Day -1 to Day 3) and a post-study follow-up telephone call (about 4-11 days after discharge from the clinical unit). During each assessment day, participants will use one of the two variants of the Logic Compact e-liquids. During each period, participants will be asked to complete two use sessions per day, one session where participants will use the product for a period of 5 minutes and a second use session where participants will be required to use the product as they feel necessary for a period of up to 6 hours. During each session, blood samples will be taken to measure the levels of nicotine in the blood, how these change over time and to measure how these levels vary between the two products in single use and multiple use of the product. In addition, participants will be asked to complete a series of questionnaires in order to assess different measures such as product satisfaction 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. A total of about 93 ml of blood will be taken. Blood sampling may cause discomfort, bruising, bleeding and/or soreness at or around the area of needle insertion site. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. Measuring blood pressure and pulse rate may cause mild discomfort in the arm whilst the cuff is inflated. Performing the lung function tests may cause some coughing, shortness of breath and light headedness.
In order to minimise the exposure risk for COVID-19 infection, participants will be required 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. At the clinical unit, participants may be asked to wear a facemask during procedures where clinical staff cannot maintain a 2 m distance. Furthermore, participants will be required to have a COVID-19 test on Day -1 of the study.
Vapour products, including electronic cigarettes, may be hazardous to health and contain nicotine which is an addictive substance. Liquid formulations (e-liquid/liquid pods) including those to be investigated in this product development study, are harmful in contact with skin or if swallowed. Whilst unlikely, there is a possibility of the devices failing, overheating or otherwise malfunctioning. E-cigarette products may harm the unborn child; therefore, pregnant and breastfeeding women are excluded from the study. All females will be required to use two effective forms of contraception during the study. This should be continued for at least 1 month after the last product use (Day 2). It is not known if e-cigarettes affect sperm or semen and therefore participants must not father a child whilst participating in the study and will be required to use two effective forms of contraception during this study until completion of the post-study follow-up phone call.

Where is the study run from?
Simbec-Orion Clinical Pharmacology Unit (UK)

When is the study starting and how long is it expected to run for?
November 2021 to February 2023

Who is funding the study?
Japan Tobacco International (Switzerland)

Who is the main contact?
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Additional identifiers

Integrated Research Application System (IRAS)
312287

Protocol serial number

JTIG-2103-GB

Study information

Scientific Title
A single-centre, single-blinded, randomized, crossover study to assess the nicotine pharmacokinetic profile following the use of two variants of the commercially available e-cigarette logic compact in adult healthy electronic cigarette users

Acronym
JTIG-2103-GB

Study objectives
To generate exploratory data with respect to the pharmacokinetic (PK) profile of nicotine and overall product assessment for two variants of Logic Compact e-liquid.

The purpose is to evaluate the concentration-time profile of nicotine in the blood during and after the use of the Logic Compact e-cigarette device and two variants of e-liquids (one with nicotine salts and one without nicotine salts) at a nicotine concentration of 18 mg/ml with two different usage regimens (5 minutes ad lib single use and 6 hours ad lib multiple use) in healthy males and females who are current daily users of any tobacco and/or non-medicinal electronic nicotine delivery products.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/03/2022, Wales Research Ethics Committee 1 Cardiff (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2920 230457, +44 (0)7787 371748, +44 (0)1792 606334; Wales.REC1@wales.nhs.uk), ref: 22/WA/0061

Primary study design
Interventional

Study design
Randomized single-blinded two-period two-sequence cross-over study

Study type(s)
Other

Health condition(s) or problem(s) studied
Alternative consumer products for current daily users of any tobacco and/or non-medicinal electronic nicotine delivery products

Interventions
Participants will be randomly allocated one of the product sequences (A-B / B-A, 10 subjects per sequence) according to a randomisation code produced by Simbec-Orion using the PROC PLAN procedure of SAS®. 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).

A. Commercially available Logic Compact Tobacco flavour, nicotine concentration: 18 mg/ml, no nicotine salts
B. Commercially available Logic Compact, Intense Amber Tobacco, nicotine concentration: 18 mg /ml, e-liquid containing nicotine salts

The products to be evaluated in this study are commercially available products registered under the Tobacco and related Products Regulations (TRPR) and the Tobacco Products and Nicotine Inhaling Products (Amendment) (EU Exit) Regulations 2020 in the UK.

This is a randomised, two-period, two-sequence, cross-over study to be conducted at a single centre. Participants will take part in two assessment days over 3 confinement days, such that each participant will receive both of the test products, one on Day 1 and one on Day 2, with the sequence determined by the randomization.

Visit 1: Medical Screening (Day -28 to Day -2)
All participants will undergo screening, which will include: administration of written informed consent, gathering of demographic, medical/surgical/social and concomitant medication histories, administration of smoking/vaping history questionnaire (including the use of tobacco and nicotine-containing products), vital signs check, blood and urine samples will be taken for standard clinical tests, electrocardiogram (ECG), spirometry testing and a physical examination with height, weight and body mass index (BMI) included. A serum pregnancy test will be performed for all females. Participants will be given the opportunity to familiarise themselves with at least one of the test products prior to enrolment. This will include formal training by study staff and a use session in order for participants to understand how the product works and to confirm that they are willing and able to use the products in the study.

Visit 2: Check-in (Day -1)
On Day -1, participants who successfully complete screening procedures will be admitted to the clinical research unit (CRU) and undergo check-in assessments. Participant eligibility will be re-confirmed and participants will receive either a COVID-19 polymerase chain reaction (PCR) antigen test or COVID-19 lateral flow test (LFT) to confirm negative status. The participants will be restricted from using any tobacco and nicotine-containing products for 12 hours prior to the single ad libitum use of the assigned product on Day 1.

Assessment Period (Day 1 and Day 2)
On each assessment day, participants will be assigned one of the test products after at least 12 hours of abstinence from nicotine-containing product use. Before, during, and for 4 hours after the start of single ad libitum use of the product for 5 minutes, blood samples will be collected to assess plasma nicotine PK (at -5, 2.5, 5, 7.5, 10, 15, 30, 60, 120, 240 min), and vital signs will be measured (at -10, 10, 30, 60, 120, 240 min). At the 10-minute time point, participants will be asked to complete questionnaires after completing other scheduled measurements (blood sampling, heart rate [HR] and blood pressure [BP] at the same timepoints.

After the 4-hour single ad libitum investigation period has ended, participants will start the multiple ad libitum use investigation period and will use the assigned product ad libitum for 6 hours. During and for 6 hours after the completion of the 4-hour single ad libitum investigational period, blood samples will be collected to assess plasma nicotine PK (at 6, 8, and 10 hours), and participants will complete subjective effects questionnaires (at 10 hours).
After completion of the multiple-use investigation period, participants will be asked to abstain from any tobacco and nicotine products use for 12 hours prior to the next single ad libitum investigational period or discharge.

Adverse events (AEs) and concomitant medication information will also be collected during the assessment periods.

Check-out (Day 3):
All participants will be checked out on Day 3 after vital signs measurements, collection of samples for standard clinical labs, ECG and a physical examination. Participants may reside at the clinic for additional days for safety observation at the discretion of the Investigator.

Follow-up Telephone Call:
Participants will be given a safety follow-up telephone call to record any use of concomitant medication and/or occurrence of AEs 4-11 days following Check-out or withdrawal.
The study end is defined as 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
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Logic Compact Tobacco flavour, Logic Compact Intense Amber Tobacco

Primary outcome(s)
Nicotine pharmacokinetic (PK) parameters following single and multiple ad libitum use of two variants of the commercially available e-cigarette Logic Compact pods. The parameters to be calculated are as follows:
1. Maximum observed plasma nicotine concentration (Cmax, single) following a single ad libitum use
2. Area under the plasma nicotine concentration versus time curve from time zero to 240 min post-start of a single ad libitum use (AUC0-240)
3. Time of maximum observed plasma concentration (tmax, single) following a single ad libitum use
4. Maximum plasma nicotine concentration (Cmax, multi) following a multiple ad libitum use

Assessment Days 1 & 2: Blood samples will be taken at the following timepoints: 5 min, 2.5 min, 5 min, 7.5 min, 10 min, 15 min, 30 min, 60 min, 120 min, 240 min & at 6 h, 8 h, and 10 hours following the start of 5-minute single ad libitum use session on each day

Key secondary outcome(s)
1. Subjective effects measured using Subjective Effects Questionnaires at 10 min and 10 hours following the start of 5 minute single ad lib use session on each day
2. Heart rate and blood pressure measured using DINAMAP* Compact Vital Signs Monitor (Model TS) 10 minutes prior to the start of single ad libitum use, and at 10 min, 30 min, 60 min, 120 min, 240 minutes and 10 hours following the start of 5 minute single ad lib use session on each day
3. Theoretical consumed nicotine measured using product weight prior to and following

completion of each single ad lib use and multiple ad lib use session on each day
4. Adverse events (AEs) collected from informed consent through to the post-study telephone call
5. Intent to use the product again measured using the visual analogue scale (VAS) after single and multiple ad libitum use
6. Satisfaction, psychological rewards, aversion, enjoyment of respiratory tract sensations and craving reduction measured using subscales of the modified Product Evaluation Scale (mPES) after single and multiple ad libitum use

Physiological endpoint:
1. Blood pressure (BP) and heart rate (HR) measured using DINAMAP* Compact Vital Signs Monitor (Model TS) at baseline and up to 240 minutes following the start of single ad libitum use

Safety endpoints:
1. Overall physical health measured using physical examination at screening, Day -1 & Day 3 (prior to discharge)
2. Vital signs (except physiological endpoints) measured using DINAMAP* Compact Vital Signs Monitor (Model TS) at screening, Day -1 & Day 3 (prior to discharge)
3. ECG parameters measured using 12-lead electrocardiogram (ECG) at screening, Day -1 & Day 3 (prior to discharge)
4. Laboratory safety parameters measured using clinical laboratory evaluations at screening, Day -1 & Day 3 (prior to discharge)
5. AEs/serious adverse events (SAEs) using ad hoc reporting and non-leading questioning of participants throughout the study from informed consent through to the post-study telephone call

Other endpoint:
1. Theoretical amounts of consumed nicotine following single ad libitum use and multiple ad libitum use. Estimations of theoretical consumed amount of nicotine will be calculated from the weight changes of the investigational product (Pods containing e-liquid) before and after participant’s single and multiple ad libitum use.

Completion date
23/02/2023

Eligibility

Key inclusion criteria
1. Male or female aged from 19 to 65 years at Screening Visit
2. Participant lives in the UK
3. Participant is able to read, understand and sign a Patient 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 a tobacco or nicotine containing product user for 12 months and have been using a commercially available, nicotine-containing closed tank/cartridge e-cigarette (in which the e-liquid contains nicotine up to 20 mg/ml), daily for at least 3 months prior to the Screening Visit
6. Participant has positive urine cotinine tests (> 200 ng/mL) at Screening Visit and Check-in
7. Participant is a healthy participant, as judged by the Principal Investigator, based on all available assessments at 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

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 two effective forms of contraception from the time of signing the ICF until 1 month following the last product use session on Day 2 or be surgically sterile for at least 3 months prior to the Screening Visit.
10. Male participant (and partner of childbearing potential) willing to use two effective forms of contraception (see Section 10.5.1), 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 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, prior to enrolment, is not planning to quit/reduce their cigarette/nicotine usage in the next 4 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

Sex
All

Total final enrolment
20

Key exclusion criteria
1. As per Principal Investigator judgment, the participant cannot participate in the study for any reason (e.g., medical, psychiatric, poor peripheral venous access, and/or social reason)
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 Principal Investigator judgment, the participant has medical conditions which required or in the course of the study would have required, a medical intervention (e.g., the start of treatment, surgery, hospitalization) 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. Participants who have an acute illness (e.g., upper respiratory tract infection, viral infection, etc) requiring treatment within 4 weeks prior to 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 prior to Check-in
8. Participant has received medication (prescription or over-the-counter [OTC] – not including COVID-19 vaccination which is allowed during the study duration) within 14 days or within 5 half-lives of the drug prior to Check-in that had an impact on 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 e-cigarette in which e-liquid contains cannabis within 3 months prior to Check-in
12. Participant has positive serology test for human immunodeficiency virus (HIV) 1/2, hepatitis B, or hepatitis C
13. Participant violates local rules of blood donation in terms of acceptable amounts of blood drawn in a certain period of time, due to blood sampling in this study
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 the 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
29/03/2022

Date of final enrolment
25/04/2022

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
Japan Tobacco (Switzerland)

ROR
https://ror.org/04f5ks076

Funder(s)

Funder type
Industry

Funder Name
Japan Tobacco

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing statement as of 22/08/2022:
The raw participant-level datasets (those used to construct the TFLs) are not likely to be made available in the registry. The summary of the aggregated participant data (as presented in the summary tables of the CSR) will be published as part of the results uploaded onto the registry and this would be deemed a sufficient representation of the overall trial data. In addition, the boundaries of the participant consent do not permit for the sharing of individual data (even pseudonymised), the consent is covered for a summary of the data in a report, sharing with the sponsor and regulatory authorities as needed and sharing with any entities working on behalf of the sponsor.

Previous IPD sharing statement:
The study data will be shared with relevant research groups and external stakeholders collaborating with the study sponsor to support the future development of the IMP 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	14/03/2023	15/03/2023	No	No
HRA research summary			28/06/2023	No	No