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A study to investigate chemical compounds in healthy adults' exhaled breath following e-cigarette use

Submission date	Recruitment status	[_] Prospectively registered
26/10/2020	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
27/11/2020	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
06/02/2023	Other	

Plain English summary of protocol

Background and study aims

The purpose of this exploratory research study is to investigate, measure and analyse the different levels of certain chemicals which are used to make up e-liquids or are produced when the e-liquid is heated. The study will provide some early high-level data from a small group of participants to investigate the exposure of the users to these particular chemicals. These chemicals will be measured in the breath after using the e-cigarette device on 4 occasions (known as product use periods) with 2 different types of vaping technique i.e. mouth holding and inhalation.

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 study sponsor intends to conduct this initial exploratory research in order to generate high-level data to specifically measure the levels of certain chemicals which are found within the e-liquids or produced following heating of the e-liquid.

It is known that inhalation of these chemicals into the mouth and lungs (also known as volatile organic compounds or VOCs) can have a significant impact on health if they are inhaled in large enough amounts or concentrations.

Therefore, it is important to measure the levels of these chemicals and to determine whether and to what degree these chemicals and their constituents pass from the user into their exhaled breath.

The test product (Logic Compact e-cigarette device and Tobacco flavour pods, nicotine concentration 12 mg/ml) is available for purchase in the UK.

Who can participate?
A total of 6 participants are needed for this study. Participants may be males or females aged between 19 and 65 years of age who are current daily users of tobacco/non-medicinal nicotine-containing products (with at least 12 months of consistent use) 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), 4 product use periods (a total of 1 day in the clinical unit with no overnight stays) and a safety follow up phone call. There are 4 product use periods in total where participants use the e-cigarette under different vaping regimes i.e. mouth holding or inhalation. At each product use period, participants will be required to exhale into a device which will measure the level of different chemicals in the breath produced by the e-liquid and e-cigarette device.

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:
1. Blood sampling: A total of approximately 7.5 ml blood will be taken. This procedure 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.
2. Blood pressure and pulse rate: This procedure may cause mild discomfort in the arm whilst the cuff is inflated.
3. Spirometry: Performing the lung function tests may cause some coughing, shortness of breath and lightheadedness.
4. In order to minimise 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.

E-Cigarette Product Use
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. While unlikely, there is a possibility of the devices failing, overheating, or otherwise malfunctioning.

Contraception
The e-cigarette product might harm the unborn child; therefore pregnant and breastfeeding women are excluded from the study. All females will be required to use 2 reliable and effective forms of contraception during the study. This should be continued for at least 1 month after the last product use (Day 1). It is not known if the study product will affect sperm or semen and therefore participants must not father a child during this study or 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?
August 2020 to September 2020

Who is funding the study?
JT International SA (Switzerland)

Who is the main contact?
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Contact information

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Additional identifiers

Integrated Research Application System (IRAS)
271631

Study information

Scientific Title
An exploratory research study to evaluate the concentration of volatile organic compounds in exhaled breath following use of the logic compact e-cigarette and tobacco flavour pod in healthy males and females who are current daily users of any tobacco and/or non-medicinal electronic nicotine delivery products.

Acronym
JTIG-1901-GB

Study objectives
There is a limited impact on the volatile organic compound profile in exhaled breath from the use of different vaping regimes, inhalation versus mouth holding.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/06/2020, London - South East Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8085; londonsoutheast.rec@hra.nhs.uk), REC ref: 20/HRA/2098

Primary study design
Interventional

Study design
Single centre open-label non-randomized four-period exploratory study

Study type(s)
Other

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

Interventions
Screening (Days -28 to Day -1):
Screening assessments will be performed from Days -28 to Day -1, to ensure the eligibility of participants. Subjects will be selected for participation based on medical history, informed consent, demographics, height, weight, Body Mass Index (BMI), nicotine use status/history, physical examination, vital signs, 12-lead electrocardiogram (ECG), lung function test, biochemistry (including serum pregnancy tests on all female subjects and follicle stimulating hormone (FSH) for postmenopausal females only), haematology and urine drugs of abuse (DOA) (including alcohol) screen. In addition, participants will also be asked to trial the Logic Compact E-cigarette and Tobacco flavour pod for a maximum of 10 minutes ad libitum during their Screening Visit, to confirm that the participant is willing to use the product on Day 1.

Day 1 Study Visit:
Eligible participants will attend the Clinical Pharmacology Unit once on Day 1 for approximately 7-9 hours, the drugs of abuse (including alcohol) and pregnancy (for all female subjects) tests will be repeated and a symptom-driven physical examination will be completed where required; the continued eligibility of each subject will be assessed by an Investigator.

On Day 1, after a minimum of 2-hour nicotine abstinence, eligible subjects will be asked to use the study product during each of the four study periods (new Tobacco flavour pod with full-charged Logic Compact E-cigarette device will be provided for each period) using the Logic Compact E-cigarette and Tobacco flavour pod with a nicotine concentration of 12 mg/mL

according to controlled product usage regimes (either mouth-holding or inhalation).
There will be a 2-hour (minimum) washout period between the end of product use in the current period (either period 1 or 2) and the start of product use in the next period (either period 2 or 3). Then, there will be a 30-minute (minimum) washout period between the end of the product use in period 3 and the start of the product use in period 4. The proton transfer reaction time-of-flight mass spectrometer (PTR-TOF-MS) mouthpiece will be changed for each period as a minimum and on an Adhoc basis.

Day 1 Period 1:
Prior to product use (N.B. to be completed within 5 minutes pre-product use), participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 30 seconds for 5 minutes. During the 5-minute product use session, all exhaled breath will be collected for measurement of VOCs concentration via the inhalation regime. The participants will be asked to puff on the e-cigarette every 30 seconds for approximately 4.5 minutes (total of 10 puffs) and to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument following each inhalation. Upon completion of the product use session, participants will be asked to keep exhaling into the instrument every 20 seconds for 5 minutes up to the 10-minute timepoint. Following the 10-minute timepoint, participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 20 seconds for 2 minutes at the following timepoints: 20, 30, 40, 50, 60, 90 and 120 minutes.

Day 1 Period 2:
Prior to product use (N.B. to be completed within 5 minutes pre-product use), participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 30 seconds for 5 minutes. During the 5-minute product use session, the participants will be asked to puff on the e-cigarette every 30 seconds for approximately 4.5 minutes (total of 10 puffs) via the mouth holding regime and to exhale into the open air following each inhalation. Upon completion of the product use session (following exhalation of the final (10th puff) into the open air), participants will be asked to immediately begin exhaling through a disposable mouthpiece into the PTR-TOF-MS instrument every 20 seconds for 5 minutes up to the 10-minute timepoint. Following the 10-minute timepoint, participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 20 seconds for 2 minutes at the following timepoints: 20, 30, 40, 50, 60, 90 and 120 minutes.

Day 1 Period 3:
Prior to product use (N.B. to be completed within 5 minutes pre-product use), participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 30 seconds for 5 minutes. During the 5-minute product use session, exhaled breath will be collected for measurement of VOCs concentration via the inhalation regime. The participants will be asked to puff on the e-cigarette every 30 seconds for approximately 4.5 minutes (total of 10 puffs) and to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument following each inhalation. Upon completion of the product use session, participants will be asked to keep exhaling into the instrument every 20 seconds for 5 minutes up to the 10-minute timepoint. Following the 10-minute timepoint, participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 20 seconds for 2 minutes.

Day 1 Period 4:
Prior to product use (N.B. to be completed within 5 minutes pre-product use), participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 30 seconds for 5 minutes. During the 5-minute product use session, exhaled breath will be collected for measurement of VOCs concentration via the mouth-holding regime. The participants will be asked to puff on the e-cigarette every 30 seconds for approximately 4.5 minutes (total of 10

puffs) and to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument following each inhalation. Upon completion of the product use session, participants will be asked to keep exhaling into the instrument every 20 seconds for 5 minutes up to the 10-minute timepoint. Following the 10-minute timepoint, participants will be asked to exhale through a disposable mouthpiece into the PTR-TOF-MS instrument every 20 seconds for 2 minutes.

In periods 3 and 4, participants will be asked to exhale into the instrument (PTR-TOF-MS) via dilution system to enable the analysis of the concentrations of exhaled VOCs for each vaping regimen before and during using e-cigarette.

During each of the four periods on Day 1, the following basic measures will be captured; start time of the measurement (taken from PTR-TOF-MS instrument), the cycle number of the first exhalation of the "background" measurement (prior to product use) (taken from PTR-TOF-MS instrument), the cycle number of the first exhalation after starting product use (taken from PTR-TOF-MS instrument), number of inhalations and exhalations, device ID, total number of device and pods used, start & final weight of device in situ and start time for first exhalation of each timepoint.

Adverse events (AEs) and concomitant medication usage will be recorded throughout the study. Subjects will remain in the Clinical Pharmacology Unit until Day 1 Period 4 has been completed. Following completion of all four periods, or upon subject withdrawal, participants will be asked whether they are experiencing any symptoms or complaints. Any AEs will be recorded in the case report form (CRF) and followed up as necessary by the Investigator.

Follow-up telephone call (5-7 days following Day 1 Study Visit):
A post-study follow-up telephone call will be performed 5 to 7 days following the Day 1 study visit/product use. A follow-up of any adverse events experienced, and concomitant medication administered will be conducted. These will be recorded in the CRF and followed up as necessary by the Investigator. Up to 2 documented attempts will be made to contact the subjects.

All Serious Adverse Events (SAEs) and all AEs that have not resolved by the end of the study will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change, whichever is earlier. This may involve the subject making additional visits to the site.

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 E-cigarette and Tobacco flavour pod, nicotine concentration: 12 mg/ml

Primary outcome(s)

The concentration-time profiles of propylene glycol (PG) in exhaled breath following the use of a Logic Compact E-cigarette and Tobacco flavour pod under two fixed-vaping regimens. This will be measured through exhalation into a PTR-TOF-MS instrument at the following timepoints:

Product Use Periods 1 & 2: 5 minutes prior to product use, each exhalation during product use (Period 1 only) , 5 mins, 10 mins, 20 mins, 30 mins, 40 mins, 50 mins, 60 mins, 90 mins, 120 mins post-product use*
Product Use Periods 3 & 4: 5 minutes prior to product use, each exhalation during product use, 5 mins, 10 mins post-product use*
*At each timepoint listed above, participants are required to breathe into the machine once every 20 seconds for a 2-minute period. For periods 3 and 4, participants are required to breathe into the machine every 20 seconds for a period of 5 minutes.

Key secondary outcome(s)
1. Concentration-time profiles for the following volatile organic compounds (VOCs): vegetable glycerol (VG), nicotine, phenyl carbinol, pyrazines (2, 3, 5-trimethylpyrazine), vanillin (vanillin PG acetals), theobromine, ethanol, methyl cyclopentenolone, propenyl guaethol measured using PTR-TOF-MS at the timepoints listed below
2. The pharmacokinetic parameters derived from concentration-time profiles of PG, VG and nicotine in exhaled breath following the use of a Logic Compact E-cigarette and Tobacco flavour pod under two fixed-vaping regimens using Phoenix WinNonLin
3. The theoretical consumed amounts of PG, VG and nicotine using PTR-TOF-MS at the timepoints listed below
4. Potential adverse events and concomitant medication whilst using and/or following use of the Logic Compact E-cigarette and Tobacco flavour pod with a nicotine concentration of 12 mg/ml recorded from the time of informed consent to post-study follow-up phone call.

Product Use Periods 1 & 2: 5 minutes prior to product use, each exhalation during product use (Period 1 only) , 5 mins, 10 mins, 20 mins, 30 mins, 40 mins, 50 mins, 60 mins, 90 mins, 120 mins post-product use*
Product Use Periods 3 & 4: 5 minutes prior to product use, each exhalation during product use, 5 mins, 10 mins post-product use*
*At each timepoint listed above, participants are required to breathe into the machine once every 20 seconds for a 2-minute period. For periods 3 and 4, participants are required to breathe into the machine every 20 seconds for a period of 5 minutes.

Completion date
11/09/2020

Eligibility

Key inclusion criteria
1. Healthy male or female subject who are current daily users of any tobacco and / or non-medicinal electronic nicotine delivery products., between 19 and 65 years of age, inclusive. Age verification will be performed by checking valid forms of government-issued identification (e.g., passport, driving licence or validate UK card) during Screening.
2. Female subject of childbearing potential willing to use 2 effective methods of contraception, i. e., established method of contraception + condom, if applicable (unless of non-childbearing potential or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from the first dose until 1 month after the last dose of IP.
3. Female subject of non-childbearing potential. For the purposes of this study, this is defined as

the subject being amenorrhoeic for at least 12 consecutive months or at least 4 months post-surgical sterilisation (including bilateral fallopian tube ligation or bilateral oophorectomy with or without hysterectomy).
4. Female subject with a negative pregnancy test at Screening Visit and before the first dose administration of the IP on Day 1.
5. Female subject of post-menopausal status confirmed by demonstrating at Screening Visit that the serum level of the follicle-stimulating hormone (FSH) falls within the respective pathology reference range. In the event a subject's menopausal status has been clearly established (for example, the subject 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 subject's eligibility to be included in the study will be at the Investigator's discretion following consultation with the Sponsor.
6. Male subject willing to use 2 effective methods of contraception, i.e., established method of contraception + condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the subject) from Day 1 visit until completion of the Follow Up Phone Call.
7. Subject with a BMI of ≥ 18.0 or ≤32.0 kg/m2
8. Prior to study start, subjects must be a self-reported current daily user of any tobacco and/or non-medicinal electronic nicotine delivery product (with at least 12 months of consistent use), who are not intending to make a quit attempt, change / alter their tobacco or nicotine usage during the study and up to completion of the post-study telephone follow-up call that can tolerate an e-liquid concentration of up to 18 mg/mL prior to the Screening Visit. This should include conventional cigarette smokers, e-cigarette users, roll-your-own cigarette smokers or dual users (of either conventional cigarette and/or roll-your-own cigarette smokers and e-cigarette users).
9. No clinically significant abnormal laboratory test results (in the opinion of the investigator) for serum biochemistry and haematology within 28 days before receiving the first dose administration of the IP.
10. Subject with a negative urinary DOA screen (including alcohol) test results, determined within 28 days before the first dose administration of the IP unless there is a documented medical explanation for the positive result other than drugs of abuse (e.g., the subject has been prescribed opioids for pain). (N.B.: A positive test result may be repeated at the Investigator's discretion).
11. Subject with no clinically significant abnormalities in 12-lead electrocardiogram (ECG) or vital signs determined within 28 days before first dose of IP.
12. Subject must be willing to comply with all required study procedures and be available to complete the study (including all follow up visits).
13. Subject must be able to safely perform all required study procedures, as determined by the Investigator.
14. Subject must be willing to consent to have data entered The Over-volunteering Prevention Service (TOPS).
15. Subject must be able to read, understand, and willing to sign an Informed Consent Form (ICF) and provide written informed consent to participate in the study.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
6

Key exclusion criteria
1. Subject who is a menthol cigarette smoker or menthol e-cigarette user
2. Subject who is a snuff or snus tobacco user
3. Subject who has any clinically relevant abnormal findings on the physical examination, medical history, lung function tests, 12-lead ECG, or clinical laboratory evaluations, unless deemed not clinically significant by the investigator or their appropriately qualified designee
4. Subject who has, or who has had a relevant history of any clinically significant: neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, or haematological conditions and/or other significant medical conditions including, without limitation, those pertaining to COVID-19 that, in the opinion of the Investigator or their appropriately qualified designee, would jeopardise the safety of the subject, safety of anyone involved in the study or impact on the validity of the study results
5. Subject who has used prescription or over-the-counter bronchodilator medication (e.g. inhaled or oral β-adrenergic agonists) to treat a chronic condition within the 12 months prior to Screening visit
6. Subject who has received any medications or substances (other than tobacco) which are known to be strong inducers or inhibitors of cytochrome P450 (CYP) and CY2A6 enzymes within 14 days (or 5 half-lives (whichever is longer) prior to Screening
7. Subject who has a clinically significant acute illness (e.g., respiratory tract infection) requiring treatment within 4 weeks prior to first dose
8. Subject who, prior to enrolment, is planning to quit/reduce their tobacco/nicotine usage during the study and up to completion of the post-study telephone follow-up call. All subjects will be informed that they are free to quit nicotine use and withdraw from the study at any time
9. Subject who has had any treatment with smoking cessation medications (e.g., Bupropion, Champix or any nicotine replacement therapies (NRTs)) within 8 weeks of the planned first nicotine dosing occasion
10. Subject who is unwilling to trial the study product during their Screening and/or Day 1 Visit
11. Female subject who is pregnant or breastfeeding or intending to become pregnant during the course of the study. This will be confirmed with a pregnancy test performed at Screening and before the first product use. and on Admission. Any female subject who becomes pregnant during this study will be withdrawn
12. Subject is a current or former employee of the tobacco and vaping industry or is a first-degree relative (parent, sibling, child)
13. Subject with a known allergy to the components of the Investigational Products
14. Subject who is unable or unwilling to participate in the Day 1 visit
15. Participation in a New Chemical Entity clinical study within the previous 3 months or a marketed drug clinical study within the 30 days before the Day 1 visit (washout period between studies is defined as the period of time elapsed between receiving the last dose of the previous study and receiving the first dose of the next study)
16. Subject who, in the opinion of the Investigator, is unsuitable for participation in the study

17. A clinically significant history of drug or alcohol abuse [defined as the regular consumption of more than 14 units for male and female subjects) of alcohol a week] within the past 2 years
18. Inability to communicate well with the Investigators (i.e., language problem, poor mental development or impaired cerebral function)
19. Donation of 450 ml or more blood within the 3 months before the first dose of IP

Date of first enrolment
17/08/2020

Date of final enrolment
24/08/2020

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec-Orion Clinical Pharmacology (AKA Simbec Research Ltd)
Simbec-Orion Clinical Pharmacology
Merthyr Tydfil Industrial Park
Cardiff Road
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Sponsor information

Organisation
JT International SA

Funder(s)

Funder type
Industry

Funder Name
JT International SA

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. At the point that the results for the study are collated into a formal study report, we will upload the relevant datasets into the registry. These datasets will be uploaded in a pseudonymised form, using only the subject number assigned to each participant in the study. No personally identifiable information will be provided as part of the results upload.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results	version 1.0	01/11/2021	01/11/2021	No	No
HRA research summary			28/06/2023	No	No