ISRCTN80837297 https://doi.org/10.1186/ISRCTN80837297

A study to investigate the effect of different variations of eLiquid on the nicotine concentration in the blood when compared to a conventional cigarette

Submission date
19/10/2020

Recruitment status
No longer recruiting

Registration date
03/11/2020

Overall study status
Completed

Last Edited
04/07/2023

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Electronic cigarettes (eCigarettes) are a rapidly evolving product category that are used to deliver nicotine to a consumer as an alternative to combustible cigarettes. The improvements made in the products are intended to deliver nicotine in a way comparable to a combustible cigarette, therefore being a suitable alternative to cigarettes. The aim of this study is to evaluate how different eLiquid formulations impact the nicotine levels in the blood compared to each other and a cigarette.

Who can participate?
Healthy males and females between the ages of 21 and 60, who are regular users of eCigarettes and factory-made cigarettes.

What does the study involve?
Participants will be screened to ensure they are healthy and use both cigarettes and eCigarettes. Participants will arrive at the clinic facility for an eight-night stay. On the day of arrival, participants will have a chance to familiarise themselves with the test eLiquids. Over the next eight days, participants will use each of the eight test products (seven eLiquids and their regular cigarette), with one product being used each day. Products will be assigned in a random order for testing. When assigned an eCigarette, participants will have two 10-minute sessions: one where participants will use the products in a pre-defined way (fixed-puff), and one where participants will use the products as they wish (ad-libitum). The two sessions will be separated by a six-hour period where participants will not be able to use nicotine products. When assigned the cigarette, participants will have one 10-minute session, where participants will smoke the cigarette as they wish (ad-libitum). Before, during and up to one hour after the product use session, participants will have a small amount of blood taken, and their heart-rate measured. Participants will also complete a product satisfaction questionnaire. Between the use of

different products, participants will not be able to use nicotine products for 12 hours before the first testing session. Approximately one week after leaving the clinic, participants will have a follow-up telephone call.

What are the possible benefits and risks of participating?
There are no direct benefits to participants for taking part. 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 from this study may provide information for the sponsor as to which eCigarette products are the most satisfying/effective for consumers. The main risks are the side-effects with using nicotine products (such as headache, dizziness, palpitations, mouth and throat irritation), which participants are familiar with from being regular users.

Where is the study run from?
The study will take place at Simbec Orion (Merthyr Tydfil, Wales, UK)

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

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

Who is the main contact?
Justin Frosina
justin_frosina@bat.com

Contact information

Type(s)
Public

Contact name
Mr Justin Frosina

Contact details
British American Tobacco
Regents Park Road
Southampton
United Kingdom
SO15 8TL
+44 (0)2380588108
justin_frosina@bat.com

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

289176

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
BAT4120024/ RD 683-34979, IRAS 289176

Study information

Scientific Title
A randomised, controlled, open-label, crossover study to assess the nicotine pharmacokinetic profile of different eLiquid formulations delivered by an eCigarette in healthy adult subjects

Study objectives
1. Different eLiquid formulations results in different plasma nicotine compared to the control formulation
2. Higher concentrations of nicotine in the eLiquid increases the level of plasma nicotine compared to lower concentrations
3. A fixed puffing protocol yields a different plasma nicotine PK profile to that of an ad libitum puffing protocol
4. The plasma nicotine of each eCigarette are not higher than those obtained from a cigarette

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/10/2020, Wales Research Ethics Committee 1 (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)7973 687815; Wales.REC1@wales.nhs.uk), ref: 20/WA/0264

Study design
Single-centre interventional randomised controlled open-label crossover study

Primary study design
Interventional

Secondary study design
Randomised cross over 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
Effect of different variations of eLiquid on the nicotine concentration in the blood

Interventions
The products to be investigated in this study are as follows:
EPOD2.0_VFB50_1VA (Control 1)
EPOD2.0_VFB35_3VE (Control 2)
Participants own brand cigarette (Control 3)
EPOD2.0_VFB35_2VB (Intervention 1)
EPOD2.0_VFB50_2VH (Intervention 2)
EPOD2.0_VFB50_3VF (Intervention 3)
EPOD2.0_VFB50_3VJ (Intervention 4)
EPOD2.0_VFB50_2VI (Intervention 5)

Each participant will use eCigarette products for two 10-minute sessions - The first will be in a fixed-puffing regimen (1 puff every 30 seconds for 10-minutes). The second will be in a ad-libitum puffing regimen (puffing as participants feel necessary for 10-minutes).

Participants will use cigarettes for 10-minutes in an ad-libitum puffing regimen only.

The order of product use will be randomised (Williams Latin square design), with a 12-hour abstinence period observed between each product use. For eCigarettes, each session will be separated by a 6-hour abstinence period.

Following discharge, a phone-follow up will occur one week later.

Intervention Type
Other

Primary outcome measure
Plasma nicotine is measured using a validated LC-MS/MS method at -5 (pre-dose), 5, 8, 10, 15, 30 and 60 minutes post-dose relative to “first puff” of product.

Secondary outcome measures
1. Heart rate will be measured by telemetry at -5 (pre-dose), 5, 8, 10, 15, 30 and 60 minutes post-dose relative to “first puff” of product
2. Product satisfaction measured using a subjective product satisfaction questionnaire at 60 minutes post first-puff
3. Product use is measured gravimetrically pre and post puffing session

Overall study start date
07/09/2020

Completion date
28/02/2021

Eligibility

Key inclusion criteria
To be confirmed at screening:
1. Healthy male or female subject, between 21 and 60 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 a highly effective method of contraception or 2 effective methods of contraception, 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
5. Female subject 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 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. Subject with a bodyweight exceeding 52kg (males) or 45kg (females) and a body mass index (BMI) of 18.5 - 32 kg/m2. BMI
7. No clinically significant history of previous allergy/sensitivity to Nicotine or any of the excipients contained within the IP(s)
8. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 30 days before the first dose administration of the IP
9. Subject with a negative urinary drugs of abuse (DOA) screen (including alcohol) test results, determined within 30 days before the first dose administration of the IP (N.B.: A positive alcohol test result may be repeated at the Investigator's discretion)
10. Subject with negative human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg)) and hepatitis C virus antibody (HCV Ab) test results at Screening
11. No clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 30 days before the planned first nicotine dosing occasion
12. No clinically significant abnormalities in vital signs (blood pressure, pulse rate, and oral temperature) determined within 30 days before the planned first nicotine dosing occasion
13. Subject with an acceptable lung functions test as determined by the PI or appropriately qualified designee
14. Subject must be available to complete the study (including all follow up telephone call)
15. Subject must satisfy an Investigator about his/her fitness to participate in the study
16. Subject must provide written informed consent to participate in the study and be willing to abide by the study restrictions
17. Prior to study start, subjects must be a self-reported current regular user of eCigarettes and smokers of conventional factory-made cigarettes and must have done so for at least 1 year
18. Subject must have a screening urine cotinine level greater or equal to 200 ng/mL
19. Subjects must be smoking a maximum of 21 per week of ≥6mg ISO tar cigarettes
20. Subjects must regularly use eCigarettes with an e-liquid nicotine strength of at least 18 mg /mL
21. Subjects will be willing to use the study products (eCigarette) and use only the products provided to them during clinical confinement, and to abstain from product use when instructed
To be re-confirmed on Day -1 / prior to first dose administration:
1. Subject continues to meet all screening inclusion criteria
2. Subject with a negative urinary drugs of abuse screen (including alcohol) prior to first dose administration
3. Female subject with a negative pregnancy test

Participant type(s)
Healthy volunteer

Age group
Other

Lower age limit
21 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
32

Total final enrolment
32

Key exclusion criteria
To be confirmed at Screening:
1. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 30 days or 5 half-lives (whichever is longer) prior to the first dose of IP, unless in the opinion of the Investigator and Sponsor's Responsible Physician the medication will not interfere with the study procedures or compromise subject safety
2. Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular or metabolic dysfunction
3. A clinically significant history of drug or alcohol abuse [defined as the consumption of more than 21 units for male and 14 units for female subjects) of alcohol a week] within the past two years
4. Inability to communicate well with the Investigators (i.e., language problem, poor mental development or impaired cerebral function)
5. Participation in a New Chemical Entity (NCE) clinical study within the previous 3 months or a marketed drug clinical study within the 30 days before the first dose of IP. (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)
6. Donation of 450 mL or more blood within the 3 months before the first dose of IP, or plasma in the 7 days prior to screening or platelets in the 6 weeks prior to screening
7. Subjects who, prior to enrolment, are planning to quit smoking/vaping before the end of the follow-up period. (All subjects will be informed that they are free to quit smoking/vaping and withdraw from the study at any time)
8. Female subjects who are pregnant or breastfeeding. This will be confirmed at Screening and Admission. Any female subject who becomes pregnant during this study will be withdrawn
9. Subjects who have an acute illness (e.g. upper respiratory tract infection, viral infection, etc.) requiring treatment within 30 days prior to screening/ongoing infection at the time of admission
10. Subjects who are self-reported non-inhalers (smokers/vapers who draw smoke/aerosol from the cigarette/eCigarette into the mouth and throat but who do not inhale). Subjects who are observed as non-inhalers at Admission by the clinic staff will be excluded

11. Subjects who have a positive urine drugs of abuse or alcohol screen (confirmed by repeat) at Screening or Admission
12. Subjects who have used prescription or over-the-counter (OTC) bronchodilator medication (e.g. inhaled or oral β-adrenergic agonists) to treat a chronic condition within the 12 months prior to screening
13. Subjects who have received any medications or substances (other than tobacco) which are known to be strong inducers or inhibitors of cytochrome P450 (CYP) enzymes within 14 days or 5 half-lives of the drug (whichever is longer) prior to screening
14. Subjects who perform strenuous physical activity (exceeding the subject's normal activity levels) within 7 days prior to Screening or Admission
15. Employees and immediate relatives of the tobacco industry or the clinical site
16. Subjects who have any clinically relevant abnormal findings on the physical examination, medical history, ECG, lung function tests (During the Screening period Day-30 to Day -2) or clinical laboratory panel, unless deemed not clinically significant by the PI or the appropriately qualified designee
17. Subjects who do not use a flavoured eCigarette eLiquid
18. Subjects who have been diagnosed with a significant history of urticaria or asthma (childhood asthma is acceptable)
19. Subject who has, or who have a relevant history of any clinically significant: neurological, gastrointestinal, renal (including urinary tract infection or nephrolithiasis), 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
20. Subjects who have had any treatment with smoking cessation medications (e.g. Bupropion, Varenicline or any NRTs) within 30 days of the planned first product use occasion
21. Subjects who have previously been diagnosed with any form of malignancy (except basal cell carcinoma, fully removed)
22. Subjects who have previously randomised into or withdrawn from this study
23. Subjects who, in the opinion of the PI or the appropriately qualified designee, should not participate in this study
24. Subjects with a positive COVID-19 PCR (Antigen) test on admission (Day-1) if required /indicated
To be re-confirmed at Day -1/prior to first dose administration:
1. Development of any exclusion criteria since the Screening visit
2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements since Screening, unless in the opinion of the Investigator and Sponsor's Responsible Physician, the medication will not interfere with the study procedures or compromise subject safety
3. Participation in a clinical study since the Screening visit
4. Donation of 450 mL or more blood since the Screening visit
5. A positive COVID-19 PCR (Antigen) test at admission (day-1) if required/indicated

Date of first enrolment
16/11/2020

Date of final enrolment
13/01/2021

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec Orion
Merthyr Tydfil Industrial Park
Merthyr Tydfil
United Kingdom
CF48 4DR

Sponsor information

Organisation
British American Tobacco (United Kingdom)

Sponsor details
Regents Park Road
Southampton
United Kingdom
SO15 8TL
+44 (0)2380588108
justin_frosina@bat.com

Sponsor type
Industry

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

ROR
https://ror.org/01znsh139

Funder(s)

Funder type
Industry

Funder Name
British American Tobacco

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Results from this study will be published in a peer-reviewed scientific journal

Intention to publish date
31/08/2023

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?
HRA research summary			28/06/2023	No	No
Results article		29/06/2023	04/07/2023	Yes	No