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A study to assess if nicotine delivered via an e-cigarette can have an effect on cognitive function in healthy adult smokers

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Registration date 07/05/2021	**Overall study status** Completed	
Last Edited 10/06/2025	**Condition category** Other	

Plain English summary of protocol

Background and aims

Reducing the negative health burden of tobacco use is a public health priority and has led to a series of regulatory and educational initiatives to encourage people not to smoke. Despite these efforts, smoking rates in adult populations worldwide remain relatively high and the World Health Organization (WHO) has forecast that there will be around 1.5 billion tobacco smokers worldwide in 2050.

It is therefore important to complement existing initiatives with strategies to attempt to reduce or prevent harm in those who will otherwise continue to smoke. Tobacco harm reduction, the substitution of cigarette smoking with potentially reduced-risk products (PRRPs), is a strategy that, if widely adopted, could offer substantial public health gains. For many years, tobacco researchers and policy experts have embraced the idea that alternative sources of nicotine, that could provide sensorial, behavioural, and physiological effects similar to smoking, might entice smokers away from combustible cigarettes. This could lead to them either quitting smoking or switching to long-term nicotine use without incurring the harm anticipated from exposure to cigarette smoke.

In the absence of both tobacco and combustion as a means of transferring nicotine, e-cigarettes deliver a vapour which is considered to contain significantly less chemical toxicants compared to cigarette smoke. An independent scientific expert panel utilized a multi-criteria decision analysis approach, incorporating aspects of harm to users, to demonstrate the potential reduction in harm of electronic cigarettes (e-cigarettes) compared to combustible cigarettes, a conclusion recently endorsed by both Public Health England and the UK Royal College of Physicians. The use of e-cigarettes to help smokers either reduce or quit smoking has been proposed as having the potential to play a major role in tobacco harm reduction, and this potential is further supported by data from large cross-sectional and longitudinal survey studies in the UK The cross-sectional data also suggest that e-cigarettes are a more effective aid to smoking cessation than more traditional nicotine replacement therapy products.

Smoking is known to have a range of physiological and psychological effects. These effects are not well understood but include effects on human cognitive function. Published scientific evidence suggests that smoking and more specifically nicotine may affect some elements of human cognitive function, including (but not limited to) sustained attention, working memory and executive function. It has been proposed that smoking cessation leads to deficits in cognitive function that can lead persons to relapse back to smoking. The ability of nicotine delivered via PRRPs to affect these parameters in a similar way to smoking has not been widely researched and may be an important aspect of the acceptability of these products to existing smokers. By replicating the physiological effects of smoking, it is anticipated that smokers, who would otherwise continue to smoke, can be encouraged to switch to PRRPs.

To determine a participant's cognitive abilities, the study will utilise the Cambridge Neuropsychological Test Automated Battery (CANTAB) Connect Profile Software, a broad digital assessment battery capable of assessing numerous elements of cognitive function. The regulatory-accepted digital tools have been utilised widely in drug development and in clinical trials for cognitive research.

The aim of this study is to determine if acute nicotine delivery (delivered via an e-cigarette) can influence attention, memory and executive function in regular smokers following a 12-hour period of nicotine abstinence in a similar manner to a combustible cigarette.

Who can participate?
Healthy adults, aged 25-45, who smoke at least 10 cigarettes per day and are familiar with e-cigarette products.

What does the study involve?
Screening assessments will be carried out within 28 days prior to the first study session. Eligible participants will be asked to attend a total of 5 testing sessions.

Following completion of the screening procedures, eligible participants will be invited to attend the first study session (approximately 1.5 days in duration, from the morning prior to the study session until the afternoon of the session day). On admittance to the Clinical Unit, participants will undergo a familiarisation period with the ePro/eCOA solution until they are comfortable with the system. Participants will complete a series of questionnaire assessing their caffeine consumption, tobacco use history and nicotine dependence (this will happen at the first study session only). Following a 12-hour overnight nicotine abstinence, participants will receive a standardised breakfast.

After a rest period, participants will complete a series of baseline questionnaires assessing their sleep quality, caffeine dependence, emotions and cigarette craving. Participants will then complete the CANTAB cognitive assessment battery. Following a second rest period participants with then use one of the study products (or no study product) for a 5 min period. Participants will then repeat the CANTAB cognitive assessment battery and repeat the questionnaires on emotions and cigarette craving. Finally, a product satisfaction questionnaire will be performed (apart from when subjects have completed the no product use session).

Participants will repeat 5 study sessions, with at least 7 days between each session, until they have used all 5 of the study products. The order in which the study products are used by each participant will be fully randomised.

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 main risks are the side-effects of using nicotine products (such as headache, dizziness, palpitations, and mouth and throat irritation); participants should be familiar with these side-effects as a result of being regular users of these products.

Where is the study run from?
Simbec Orion (UK)

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

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

Who is the main contact?
Harry Green, harry_green@bat.com

Contact information

Type(s)
Public

Contact name
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Additional identifiers

Protocol serial number
BAT4120028

Study information

Scientific Title

An exploratory, randomised, crossover study to investigate the effect of nicotine on cognitive function in healthy adult smokers who use an electronic cigarette, after a period of smoking abstinence

Study objectives
That acute nicotine delivery (delivered via an e-cigarette) can influence attention, memory and executive function in regular smokers following a 12-hour period of nicotine abstinence in a similar manner to a combustible cigarette.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/04/2021, 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: 21/WA/0095

Primary study design
Interventional

Study design
Single-centre interventional randomized partially-blinded 5-period cross over study

Study type(s)
Other

Health condition(s) or problem(s) studied
Cigarette smoking

Interventions
The order of the Investigational Product use will be randomised (using a Williams Latin square design) for this 5-period cross over study. The Investigational Products in this study are as follows:
1. No Treatment (Control 1)
2. Combustible Cigarette (Control 2)
3. EPEN3.0_VGT00 (Placebo 1)
4. EPEN3.0_VGT12 (Intervention 1)
5. EPEN3.0_VGT18 (Intervention 2)

Each participant will use the e-Cigarette or cigarette for a 5 min session of ad-libitum puffing regimen (puffing as participants feel necessary for 5 min). Participants will use one Investigational Product per study session. There will be 5 study sessions for each participant. Participants will abstain from nicotine, caffeine, and alcohol 12 h prior to the start of each study session. There will be at least 7 days between the administrations of each study session.

Intervention Type
Other

Primary outcome(s)

Current primary outcome measures as of 27/07/2021:
1. Sustained Attention as assessed via completion of the Rapid Visual Information Processing (RVP) task on the CANTAB software at baseline and immediately after product usage
2. Working Memory as assessed via completion of the Spatial Working Memory (SWM) task on the CANTAB software at baseline and immediately after product usage
3. Executive Function as assessed via completion of the One Touch Stockings of Cambridge (OTS) task on the CANTAB software at baseline and immediately after product usage
4. Episodic Memory as assessed via completion of the Paired Associates Learning (PAL) task on the CANTAB software at baseline and immediately after product usage

Previous primary outcome measures:
1. Sustained Attention as assessed via completion of the Rapid Visual Information Processing (RVP) task on the CANTAB software at 85 mins prior to and 0 mins after product usage
2. Working Memory as assessed via completion of the Spatial Working Memory (SWM) task on the CANTAB software at 85 mins prior to and 0 mins after product usage
3. Executive Function as assessed via completion of the One Touch Stockings of Cambridge (OTS) task on the CANTAB software at 85 mins prior to and 0 mins after product usage
4. Episodic Memory as assessed via completion of the Paired Associates Learning (PAL) task on the CANTAB software at 85 mins prior to and 0 mins after product usage

Key secondary outcome(s)
Current secondary outcome measures as of 27/07/2021:
1. Subjective Emotion – assessed via the Subjective Emotion Questionnaire (VAS) - at ~45 min prior to and ~40 min after product usage
2. Subjective Craving – assessed via Questionnaire on Subjective Urges (QSU) Brief – at ~45 min prior to and ~40 min after product usage

Previous secondary outcome measures:
1. Subjective Emotion – assessed via the Subjective Emotion Questionnaire (VAS) - at 45 mins prior to and 40 mins after product usage
2. Subjective Craving – assessed via Questionnaire on Subjective Urges (QSU) Brief – at 45 mins prior to and 40 mins after product usage

Completion date
27/10/2021

Eligibility

Key inclusion criteria
1. Healthy male or female subject, between 25 and 45 years of age, inclusive.
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 screening until the post study follow up phone call.
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; documentation of the procedure is required).
4. Female subject with a negative pregnancy test at Screening who is not breastfeeding or lactating.
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 body mass index (BMI) of 18.5-29.9 kg/m2; BMI = body weight (kg) / [height (m)] 2.
7. Subject with a negative urinary drugs of abuse (DOA) screen (including alcohol) test results, determined within 28 days before the first study session (N.B.: A positive test result may be repeated at the Investigator's discretion).
8. No clinically significant abnormalities in vital signs (blood pressure, pulse rate, oral temperature, respiration rate) determined within 28 days before the first study session.
9. Subjects who are self-reported current daily users of conventional factory-made cigarettes and /or roll your own cigarettes (a minimum of 10 cigarettes per day) for at least 3 years. Subjects should also be familiar with using e-cigarettes (i.e. have used e-cigarettes over a period of greater than 1 month within the last 2 years) and can tolerate an e-liquid concentration of up to 18mg/mL prior to the screening visit. 10. Product use status will be confirmed with a urinary cotinine level of ≥200 ng/mL and product use history questionnaire at screening. 10. Subjects who are willing to consume the study standardised breakfast.
11. Subjects who are willing to comply with the study protocol.
12. Subject must be available to complete the study (including all follow up visits).
13. Subject must satisfy an Investigator about his/her fitness to participate in the study.
14. Subject must provide written informed consent to participate in the study.
15. Subjects who do not have any clinically significant cognitive deficit disorders as assessed by a Medical professional and as determined by taking medical history.
16. Subjects who are willing to use a Golden Tobacco flavoured e-cigarette.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
40

Key exclusion criteria
1. Subjects 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.
2. Use of any medications or substances (other than tobacco), including vitamins, herbal and dietary supplements which are known to be strong inducers or inhibitors of cytochrome P450

(CYP) enzymes within 14 days or 5 half-lives (whichever is longer) prior to Screening.
3. Subjects who are self-reported non-inhalers (smokers/vapers who draw smoke/aerosol from the cigarette/e-cigarette into the mouth and throat but who do not inhale).
4. Subjects who, prior to enrolment, are planning to quit/alter smoking/vaping usage within the duration of the study (to follow-up telephone call). All subjects will be informed that they are free to quit smoking/vaping and withdraw from the study at any time.
5. Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular or metabolic dysfunction based on medical history.
6. A clinically significant history of drug or alcohol abuse [defined as the consumption of more than 14 units of alcohol a week for male and female subjects] within the past two years.
7. Inability to communicate well with the Investigators (i.e., language problem, poor mental development or impaired cerebral function).
8. Subjects with a positive COVID-19 PCR (Antigen) test prior to Day 1.
9. Subject with a history of allergy/hypersensitivity to any of the study products.
10. Subjects who have a diagnosis of a clinically significant cognitive disorder.
11. Subjects who have used central nervous system enhancing or modulating medications within the last 3 months and is felt to be of clinical significance by the PI (or Deputy).
12. Subjects who have colour vision deficiency as determined by an Ishihara test performed at screening.

Date of first enrolment
12/05/2021

Date of final enrolment
24/09/2021

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)

ROR

https://ror.org/01znsh139

Funder(s)

Funder type
Not defined

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

Individual participant data (IPD) sharing plan
Deidentified participant level data will be available on request from Harry Green (harry_green@bat.com). This includes all data captured using the eCRF and questionnaires and will be 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 subject to request. Requestors must sign a data access agreement.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/04/2024	10/06/2025	Yes	No
Protocol article		25/04/2022	18/08/2022	Yes	No
HRA research summary			28/06/2023	No	No