ISRCTN13625876 https://doi.org/10.1186/ISRCTN13625876

A study to assess in-the-moment product liking of a heating device with two variants of an alternative non-tobacco, nicotine-containing consumable in healthy adult heated tobacco product users

Submission date 04/01/2024	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 16/05/2024	**Overall study status** Completed	
Last Edited 18/09/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims
This study is designed to evaluate elements of abuse liability including subjective (individual) effects and physiological (bodily) measures and plasma nicotine uptake during and following ad libitum (as you desire) use of the study investigational products by generally healthy heated tobacco product (HTP) users and smokers. This study will also help provide information on how much you like the investigational product overall 4 hours after the start of investigational product use.

Who can participate?
Generally healthy male and female adult heated tobacco product (HTP) users who are also smokers of combustible cigarettes, 21 to 60 years of age (inclusive).

What does the study involve?
Staying at the research site for 6 days/5 nights.
Starting on day 2 through day 6 subjects participate in daily test sessions where they evaluate each of the investigational products in the study. The order in which they receive the investigational products will be assigned by chance, like the flip of a coin (randomization). They will be given information about the investigational product and how to use it. They will not have a choice in the order in which they will use the investigational products. They will be asked to evaluate each of the investigational products in different Test Sessions, and during each Test Session, they will evaluate only one investigational product.

What are the positive benefits and risks of participating?
Benefits:
There are no positive benefits from participating. This study is for research purposes only.

Risks:
Smoking tobacco or using tobacco products imply risks. Tobacco products are addictive. Consumption of tobacco products is associated with real risks of serious diseases.
The most common side effects related to the use of tobacco products include: cough, irritation in the mouth and throat, palpitations, feeling faint, nausea, dizziness and headache. Less common side effects include: nasal congestion, stomach discomfort, hiccups and vomiting. Even less common are: cardiac arrhythmia (irregular heartbeat).
Side effects related to the use of Heated Tobacco Product and Heated Herbal Product are the same as those of tobacco products with the most common being: dizziness and nausea, mild headache, dry mouth, dry throat, cough and diarrhoea.
Nicorette gum may cause undesirable effects like dizziness, light-headedness, or blurred vision. Common Adverse Events associated with use of nicotine gum include abnormal dreams; diarrhoea; difficulty sleeping; dry mouth; joint pain; muscle pain; nervousness; sweating; weakness.
Severe potential Adverse Events that require medical attention include severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); fast or irregular heartbeat; mouth, teeth, or jaw problems; pounding in the chest; severe diarrhoea, dizziness, nausea, vomiting, or weakness.
You may experience side effects or conditions not listed above and of which we are not aware, such as allergic reactions. Some side effects may not yet be known. In this case, you must immediately contact the study doctor at the telephone numbers listed on this information sheet.
If you are a female of childbearing potential, you must not be pregnant at the start of the trial and you must avoid becoming pregnant and you must be willing to use a form of contraception from the time of signing the informed consent until End-of-Study. If you become pregnant during the trial period despite taking precautions, it is important that you immediately notify the study doctor, who will immediately discontinue your participation in the trial.
If you are a male, you must use an acceptable method of birth control from Day 1 until the end of the trial, unless they have had a vasectomy or are abstinent from heterosexual intercourse, or their female partner is not able to bear children.

Where is the study run from?
CRC - Centro Ricerche Cliniche di Verona S.r.l. (Italy)

When is the study starting and how long is it expected to run for?
June 2023 to January 2025

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

Who is the main contact?
Linsey Haswell
linsey_haswell@bat.com

Contact information

Type(s)
Public, Scientific

Contact name
Mrs Linsey Haswell

ORCID ID
https://orcid.org/0009-0000-1457-3561

Contact details
British American Tobacco (Investments) Limited
Southampton
United Kingdom
SO15 8TL
+44 7878881232
linsey_haswell@bat.com

Type(s)
Principal investigator

Contact name
Dr Stefano Milleri

Contact details
Centro Ricerche Cliniche di Verona srl
Verona
Italy
37134
+39 045 812 6619
stefano.milleri@crc.vr.it

Additional identifiers

Protocol serial number
BAT31123039

Study information

Scientific Title
A randomised, controlled, single-centre, open-label study to assess elements of abuse liability and nicotine pharmacokinetics for a glo heating device with two variants of an alternative non-tobacco, nicotine-containing consumable in healthy adult heated tobacco product users

Acronym
veo/neo AL/PK

Study objectives
This study is being conducted to evaluate AL potential of Rooibos-based, tobacco-free heated nicotine products (HHPs). These products are intended for adult nicotine users and for smokers seeking alternatives to continued smoking supporting the British American Tobacco (BAT) mission to build A Better Tomorrow™ by reducing the health impact of the business. Rooibos (Aspalathus linearis) is a plant originating from the Western Cape of South Africa, commonly consumed as a caffeine-free herbal. It is used in a variety of consumer goods, from food to supplements as well as hand creams and shampoos. The proposed evaluation of the new HHP IPs will help identify AL and potential safety concerns associated with the consumption of these nicotine-containing products in direct comparison with a combustible cigarette (the tobacco

/nicotine product with the highest AL), and nicotine gum (one of the group of medicinal NRT products that are recognized as having the lowest AL potential among tobacco and nicotine products). This study will also help inform on the likelihood of use of HHPs and the exposure to nicotine during product use. The long-term health risks associated with cigarette smoking play a significant role in the determination that cigarettes have the highest AL among tobacco-containing products. Short-term study designs (such as that proposed here) to determine the AL of new, potentially lower-risk alternative products in comparison to conventional cigarettes (such as HHPs) provide initial information regarding the potential for the new tobacco product to be adopted by current users of combustible cigarettes.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 05/06/2024, South-West Veneto Area Regional Ethics Committee (Azienda Ospedaliera Universitaria Integrata Verona, P.Le A. Stefani, 1, Verona , 37126, Italy; +39 045 8123236; comitatoetico@aovr.veneto.it), ref: 26550

Primary study design
Interventional

Study design
Single-centre open-label randomized cross-over study

Study type(s)
Other

Health condition(s) or problem(s) studied
To assess in-the-moment Product Liking of a heating device with two variants of an alternative non-tobacco, nicotine-containing consumable in healthy adult heated tobacco product users

Interventions
Designed to evaluate elements of abuse liability (AL) including subjective effects and physiological measures (pharmacodynamics [PD]), and plasma nicotine uptake (pharmacokinetics [PK]) during and following ad libitum use of the study investigational products (IPs) by generally healthy heated tobacco product (HTP) users who also smoke combustible cigarettes.
Subjects will be randomised to a product use sequence (using a Williams Design) in which they will evaluate one IP in each of five consecutive daily Test Sessions, such that each subject will evaluate five IPs including one HTP IP, two HHP IPs, a high-AL comparator (subject's UB cigarette), and a low-AL comparator (a commercially available nicotine replacement therapy [NRT] nicotine gum).

High-AL comparator IP:
• Product A: UB filtered, Combustible Cigarette

Heated Tobacco Product (HTP) IP:
Tobacco consumable IP
• Product B: glo HTP Hyper X2 device used in Standard Mode with Redberry Click neo stick consumable, 1.7% nicotine, menthol capsule crushed

Heated Herbal Product (HHP) IPs:
Tobacco-free nicotine consumable IPs
• Product C: glo HTP Hyper X2 device used in Standard Mode with Sunset Click, a Rooibos herbal-based, tobacco-free nicotine veo stick consumable, 1.6% nicotine, menthol capsule crushed
• Product D: glo HTP Hyper X2 device used in Standard Mode with Scarlet Click, a Rooibos herbal-based, tobacco free nicotine veo stick consumable, 1.6% nicotine, menthol capsule crushed

Low- AL comparator IP:
• Product E: Nicorette® White Ice Mint 4 mg nicotine gum

Intervention Type
Other

Primary outcome(s)
Abuse Liability is measured by collecting subjective data through questionnaire responses to PL:
1. AUECPL 5-240: area-under-the-effects curve (AUEC) for PL NRS score-versus-time curve from 5 minutes to 240 minutes after the start of IP use.
2. Emax PL: maximum PL NRS score after the start of IP use.

Key secondary outcome(s)
All secondary measures were collected over a period of 4 hours during and following HTP/HHP IP use
1. Plasma nicotine uptake parameters using blood sample:
1.1. AUCnic 0-15
1.2. AUCnic 0-240
1.3. Cmax
1.4. Tmax

2. Subjective measures
Questionnaire responses to PE, UTS, OPL, OIUA:
2.1. AUECPEpos 5-240
2.2. AUECPEneg 5-240
2.3. Emax PEpos
2.4. Emax PEneg
2.5. AUECUTS 0 15
2.6. AUECUTS 0 240
2.7. Emin UTS
2.8. Eoverall PL
2.9. Eoverall IUA

3. Physiological measures
3.1. Maximum increase in blood pressure (compared to baseline) measured using a sphygmomanometer after the start of IP use.
3.2. Maximum increase in heart rate (compared to baseline) measured using a sphygmomanometer after the start of IP use.

Completion date
15/01/2025

Eligibility

Key inclusion criteria
1. Able to read, understand, and willing to sign an informed consent form (ICF) and complete questionnaires written in Italian or English.
2. Generally healthy males or females, 21 to 60 years of age, inclusive, at the time of consent.
3. Subjects who have a
3.1. body mass index (BMI) of 18.5 to 30.0kg/m², inclusive.
3.2. body weight exceeding 52kg (males) or 45kg (females).
4. Uses HTP daily and consumes an average of at least 5 HTP sticks per day.
5. Smokes combustible, filtered, factory-made cigarettes, 83 mm to 100 mm in length.
6. Smokes an average of at least 20 cigarettes per week and inhales the smoke, for at least 6 months prior to Screening. Brief periods of abstinence due to illness, quit attempt (prior to 1830 days of Screening), or clinical study participation (prior to 30 days of Screening) will be allowed at the discretion of the PI.
7. Agrees to use the same UB HTP and/or smoke the same UB cigarette throughout the study period. The UB HTP or UB cigarette is defined as the reported HTP brand currently used or cigarette brand style currently smoked most frequently, respectively, by the subject.
NOTE: HTP users or combustible cigarette smokers who also use other tobacco- or nicotine-containing products (e.g., electronic cigarettes, smokeless tobacco, and modern oral nicotine products) on no more than one day per week will not be excluded from study participation.
8. Expired breath carbon monoxide (ECO) level is ≥ 7 ppm and ≤ 100 ppm at Screening and at check-in on Day 1.
9. Positive (≥200 ng/ml) urine cotinine test at Screening.
10. Willing to use UB HTP, UB cigarette, HTP/HHP IPs, and nicotine gum during the study period.
11. Willing to abstain from tobacco and nicotine use for at least 12 hours prior to the start of each Test Session.
12. Females must be willing to use a form of contraception acceptable to the PI from the time of signing the informed consent until End-of-Study.
13. Males must use an acceptable method of birth control from Day 1 “check-in” until the end of the study, unless they have had a vasectomy or are abstinent from heterosexual intercourse, or their female partner is not able to bear children.
14. Agrees to an in-clinic confinement of 6 days (5 nights).

Participant type(s)
Population

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
21 Years

Upper age limit
60 Years

Sex
All

Key exclusion criteria

1. Presence of clinically significant uncontrolled cardiovascular, pulmonary, renal, hepatic, endocrine, gastrointestinal, psychiatric, hematological, neurological disease, or any other concurrent disease or medical condition that, in the opinion of the PI, makes the study subject unsuitable to participate in this clinical study.
2. History, presence of, or clinical laboratory test results indicating diabetes. History of gestational diabetes which is no longer present nor indicated by clinical laboratory test results is acceptable.
3. Scheduled treatment for asthma currently or within the past consecutive 12 months prior to the Screening Visit.
4. History or presence of bleeding or clotting disorders.
5. Any history of cancer, except for primary cancers of skin such as localized basal cell/squamous cell carcinoma that has been surgically and/or cryogenically removed.
6. Systolic blood pressure of > 160 mmHg or a diastolic blood pressure of > 95 mmHg, measured after being seated for five minutes at Screening and at check-in on Day 1.
7. Hemoglobin level is < 12.5 g/dL for females or < 13.0 for males g/dL at Screening.
8. Females who have a positive pregnancy test, are pregnant, breastfeeding, or intend to become pregnant during the course of the study.
9. A positive urine drug screen without evidence of prescribed corresponding concomitant medication(s) at Screening or check-in on Day 1.
10. Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
11. Use of any medication or substance that aids in smoking cessation, including but not limited to any NRT (e.g., nicotine gum, lozenge, patch), varenicline (Chantix®), bupropion (Wellbutrin®, Zyban®), or lobelia extract within (≤) 30 days prior to signing the ICF.
12. Postpones a decision to quit using tobacco- or nicotine-containing products in order to participate in this study or self-reports a previous attempt within (≤) 1830 days prior to signing the ICF.
13. Any use of aspirin (≥ 325 mg/day) or anticoagulants.
14. Individuals ≥ 35 years of age currently using systemic, estrogen-containing contraception or hormone replacement therapy.
15. Whole blood donation within 8 weeks (≤ 56 days) prior to signing the ICF.
NOTE: Subjects will be advised against scheduling a whole blood donation for at least 7 days following study completion.
16. Plasma donation within (≤) 7 days prior to signing the ICF.
NOTE: Subjects will be advised against scheduling a plasma donation for at least 7 days following study completion.
17. Employed by a tobacco or nicotine manufacturer, distributor or retailercompany, the study site, or handles tobacco- or nicotine-containing products as part of their job.
18. Participation in another clinical trial within (≤) 180 days prior to signing the informed consent. The 180-day window for each subject will be derived from the date of the last study event in the previous study to the time of signing the ICF in the current study.
19. Has a significant history of alcoholism or drug abuse within 24 months prior to Screening, as determined by the PI, or has a positive breath alcohol test at Screening or check-in on Day 1.
20. Determined by the PI to be inappropriate for this study.

Date of first enrolment
20/05/2024

Date of final enrolment
01/09/2024

Locations

Countries of recruitment
Italy

Study participating centre
CRC - Centro Ricerche Cliniche di Verona S.r.l.
Piazzale L.A. Scuro, 10,
Verona
Italy
37134

Sponsor information

Organisation
British American Tobacco (United Kingdom)

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

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to the potential of misinterpretation of data.

IPD sharing plan summary

Not expected to be made available