ISRCTN81075760 https://doi.org/10.1186/ISRCTN81075760

A study to examine health effect indicators when a smoker switches to using a tobacco heating product

Submission date
09/01/2018

Recruitment status
No longer recruiting

Registration date
31/01/2018

Overall study status
Completed

Last Edited
01/09/2022

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Cigarette smoking contributes to numerous illnesses including lung cancer, chronic obstructive lung disease and heart disease. The health risks of cigarette smoking are due to chemical toxicants in cigarette smoke which can lead to changes in the body, causing disease. Nicotine is mainly responsible for the addictive properties of cigarette smoking. The sponsor of this study is British American Tobacco (Investments) Limited, a manufacturer of tobacco products. The sponsor is developing an alternative approach to conventional (normal) cigarettes by developing new products which may reduce some of the risks of tobacco-related diseases. This study is designed for research purposes to collect data on a newly developed tobacco heating product (THP) in adult smokers. The main aim of this study is to find out whether the body is exposed to a lower amount of certain chemical toxicants from a THP as compared to smoke from regular cigarettes.

Who can participate?
Healthy volunteers aged 23 to 55, including regular smokers and people who have never smoked (smoked less than 100 cigarettes in their lifetime)

What does the study involve?
Regular smokers are randomly allocated to one of two groups (Arms A- & B) to either continue to smoke their own brand cigarettes, or to switch to smoking a THP 1.1 (RT), for 360 days. A further group (Arm D) is made up of participants who are regular smokers and who intend to quit. This group is provided with assisted smoking cessation (NRT/varenicline/counselling). The last group is made up of participants who have never smoked (Arm E). Levels of exposure to chemical toxicants are measured by testing blood and urine collected over a 24-hour period.

What are the possible benefits and risks of participating?
Participants should not expect to receive any health benefits from using the products in this study. Participants in the cessation group may expect the benefits associated with stopping smoking. The tests provided may help participants learn about their general health. They may also help participants discover an unknown medical condition. This study may help doctors,

scientists or manufacturers learn things about tobacco and nicotine products that could help others to quit smoking. Nicotine and tobacco use can have side effects but as the participants are already using tobacco products the risks related to the side effects of nicotine are low. Participants are not likely to be exposed to nicotine levels higher than the ones they are usually exposed to when smoking. The following side effects have been reported for e-cigarettes and THPs, and participants are monitored for these: headache, dizziness, palpitations, mouth and throat irritation, skin irritation, and stomach disturbances. Inhalation of too much nicotine has been reported to lead to side effects such as feeling faint, nausea or headache. Common observed side effects also include cough, irritation of the mouth or throat, dizziness, nasal congestion, stomach discomfort, hiccups and sickness (vomiting).

Where is the study run from?
1. Covance Clinical Research Unit Ltd (UK)
2. SIMBEC Research Ltd (UK)
3. Celerion (GB) Ltd (UK)
4. Richmond Pharmacology Ltd (UK)

When is the study starting and how long is it expected to run for?
February 2018 to March 2020

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

Who is the main contact?
Nathan Gale
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Contact information

Type(s)
Public

Contact name
Mr Nathan Gale

Contact details
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number
BAT3117011

Study information

Scientific Title
A randomised, controlled study to evaluate the effects of switching from cigarette smoking to using a Tobacco Heating Product on health effect indicators in healthy subjects

Study objectives
It is hypothesised that there will be a reduction in exposure to toxicants which will cause changes in health effect indicators when smokers switch to using a tobacco heating product (THP) compared with smokers who continue to smoke, and that these changes will be directionally similar to changes seen in smokers who cease smoking (assisted with NRT) over a period of 12 months in an ambulatory setting. Furthermore, it is hypothesised that reductions in toxicant levels in THP emissions will translate to sustained reductions in human exposure to cigarette smoke toxicants, as assessed by measuring biomarkers of exposure (BoE) in an ambulatory setting.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Wales Research Ethics Committee 2, 29/01/2018, REC ref: 17/WA/0212
Added 05/03/2019: Substantial Amendment approved on 01/02/2019, by same REC under same reference number.

Study design
Multi-centre randomised controlled interventional study

Primary study design
Interventional

Study type(s)
Other

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

Interventions
Current interventions as of 05/03/2019:

Three separate populations:
1. Continue to smoke / THP population
Arm A – conventional cigarettes
Arm B – THP1.1(RT)

2. Intend-to-quit population
Arm D – assisted smoking cessation

3. Never-smoked population
Arm E – never-smoked

A total of up to 510 healthy male or female subjects aged 23-55 will be enrolled on the study across 4 study arms. Up to 280 subjects will be enrolled in to study arms A and B and randomised using blocks of computer generated random number sequences in PROC PLAN by SAS®. Up to 80 subjects will be randomised to study arm A, where subjects will continue to smoke their own brand cigarettes for the duration of the study. 200 subjects will be randomised to study arm B, and will switch on study day 1 from smoking conventional cigarettes to exclusive use of a test IP (THP 1.1(RT)) for 360 days. 50 subjects are required to complete the study to 360 days in both arms.

190 subjects who intend to quit tobacco and nicotine product use will be enrolled to the cessation arm (Arm D). Cessation may be assisted with the use of NRT/varenicline/counselling at the discretion of the PI. 50 subjects are required to complete the study to 360 days in this arm.

40 subjects who have smoked less than 100 cigarettes in their lifetime will be recruited to the never smoker arm (Arm E). 30 subjects are required to complete the study to 360 days in this arm.

Follow up for all study arms will be 28 days following discharge from the clinic.

Visit 1: 0 (baseline)
Visit 2: 30 days
Visit 3: 60 days
Visit 4: 90 days
Visit 7: 180 days
Visit 10: 270 days
Visit 13: 360 days

Previous interventions:

Three separate populations:
1. Continue to smoke / THP population
Arm A – conventional cigarettes
Arm B – THP1.1(RT)
Arm C – THD2.4T20

2. Intend-to-quit population
Arm D – assisted smoking cessation

3. Never-smoked population
Arm E – never-smoked

A total of 505 healthy male or female subjects aged 23-55 will be enrolled in the study across 5 study arms. 265 subjects will be enrolled in to study arms 1-3 and randomised using blocks of computer-generated random number sequences in PROC PLAN by SAS®. 65 subjects will be randomised to study arm 1, where subjects will continue to smoke their own brand cigarettes for the duration of the study. 100 subjects will be randomised to each study arm 2 and 3, and will

switch on study day 1 from smoking conventional cigarettes to exclusive use of a test IP (THP 1 or 2) for 360 days. 50 subjects are required to complete the study to 360 days.

200 subjects who intend to quit tobacco and nicotine product use will be enrolled to the cessation arm. Cessation may be assisted with the use of NRT/varenicline/counselling at the discretion of the PI. 50 subjects are required to complete the study to 360 days.

40 subjects who have smoked less than 100 cigarettes in their lifetime will be recruited to the never smoker arm. 30 subjects are required to complete the study to 360 days.

Follow up for all study arms will be 28 days following discharge from the clinic.

Visit 1: 0 (baseline)
Visit 2: 30 days
Visit 3: 60 days
Visit 4: 90 days
Visit 7: 180 days
Visit 10: 270 days
Visit 13: 360 days

Intervention Type
Other

Primary outcome(s)
Measured using 24-hour urine ambulatory collection at visits 1, 2 ,3, 4, 7, 10, 13:
1. Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL)
2. 8-epi-prostaglandin F2α Type III (8-Epi-PGF2α Type III)

Physiological measures, measured at visits 1, 2 ,3, 4, 7, 10, 13:
1. Augmentation Index (AIx)

Key secondary outcome(s))
Current secondary outcome measures as of 05/03/2019:

Measured from 24-hour urine ambulatory collection at visits 1, 2, 3, 4, 7, 10, 13:
1. Total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates) (TNeq)
2. Total N-nitrosonornicotine (Total NNN)
3. 3-hydroxypropylmercapturic acid (3-HPMA)
4. 3-hydroxy-1-methylpropylmercapturic acid (HMPMA)
5. S-phenylmercapturic acid (S-PMA)
6. Monohydroxybutenyl-mercapturic acid (MHBMA)
7. 2-cyanoethylmercapturic acid (CEMA)
8. 1-hydroxypyrene (1-OHP)
9. 2-hydroxyethylmercapturic acid (HEMA)
10. 11-dehydrothromboxane B2 (11-dTX B2)
11. 4-hydroxy-nonenal + metabolites (4-HNE)
12. Creatinine
13. 4-aminobiphenyl (4-ABP)
14. 2-aminonaphthalene (2-AN)
15. ortho-toluidine (o-Tol)

Measured from blood samples:
1. N-(2-cyanoethyl)valine (HB [haemoglobin] adduct; CEVal) measured at visits 1, 2 ,3, 4, 7, 10, 13
2. White blood cell count (WBC count) measured at visits 1, 2 ,3, 4, 7, 10, 13
3. Monocyte chemotactic protein 1/C-C motif chemokine ligand 2 (MCP 1/CCL2) measured at visits 1, 4, 7, 10, 13
4. Soluble intercellular adhesion molecule-1 (s-ICAM1) measured at visits 1, 4, 7, 10, 13
5. Fibrinogen (Fib) measured at visits 1, 4, 7, 10, 13
6. High-sensitivity C-reactive protein (hsCRP) measured at visits 1, 4, 7, 10, 13
7. Homocysteine (HMCys) measured at visits 1, 4, 7, 10, 13
8. Glucose (Gluc) measured at visits 1, 4, 7, 10, 13
9. Plasminogen activator inhibitor-1 (PAI-1) measured at visits 1, 4, 7, 10, 13
10. Tissue plasminogen activator (tPA) measured at visits 1, 4, 7, 10, 13
11. E-Selectin (SELE) measured at visits 1, 4, 7, 10, 13
12. Endothelin-1 (ET-1) measured at visits 1, 4, 7, 10, 13
13. 3-nitrotyrosine (3-NTyr) measured at visits 1, 4, 7, 10, 13
14. Serum lipids (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol [CholTotal], triglycerides [Trigly]) measured at visits 1, 2 ,3, 4, 7, 10, 13

Measured from exhaled breath:
1. Nitric oxide (NO) measured at visits 1, 2 ,3, 4, 7, 10, 13
2. Carbon monoxide (CO) measured at visits 1 to 13

Physiological measures:
1. Blood pressure at visits 1, 2 ,3, 4, 7, 10, 13
2. Spirometry at visits 1, 2 ,3, 4, 7, 10, 13:
2.1. Peak flow
2.2. Forced vital capacity (FVC)
2.3. Forced expiratory flow (FEF) 25-75%
2.4. Forced expiratory volume in 1 second (FEV1)
3. Body weight/waist circumference at visits 1, 4, 7, 10, 13
4. Carotid/femoral pulse wave velocity at visits 1, 2 ,3, 4, 7, 10, 13
5. 6-minute walking test at visits 1, , 4, 13
6. Finger plethysmography at visits 1, 4, 7, 10, 13

Questionnaires:
1. Fagerström Test for Cigarette Dependence (FTCD) at visit 1,
2. Product satisfaction at visits 4, 7, 10, 13
3. Smoking cessation quality of life at visits 1, 4, 7, 10, 13
4. Self-reported product usage (eDiary/paper diary) recorded throughout the study from visit 1 to 13
5. Cough and Shortness of Breath VAS at visits 1, 4, 7, 10, 13

Safety:
1. Physical examination at screening and symptom-driven at visits 1,2, 3, 4, 7, 10, 13 and follow-up
2. Vital signs at screening and at visits 1, 4, 7, 10, 13 and follow-up
3. Electrocardiogram (ECG) at screening and at visits 1, 4, 7, 10, 13 and follow-up
4. Clinical laboratory evaluations at screening and at visits 1, 4, 7, 10, 13 and follow-up
5. Lung function tests at screening, visits 1, 2 ,3, 4, 7, 10, 13
6. Adverse events (AE)/serious adverse events (SAE) recorded throughout the study

Previous secondary outcome measures:

Measured from 24-hour urine ambulatory collection:
1. Total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates) (TNeq) measured at visits 1, 2 ,3, 4, 7, 10, 13
2. Total N-nitrosonornicotine (Total NNN) measured at visits 1, 2 ,3, 4
3. 3-hydroxypropylmercapturic acid (3-HPMA) measured at visits 1, 2 ,3, 4
4. 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) measured at visits 1, 2 ,3, 4
5. S-phenylmercapturic acid (S-PMA) measured at visits 1, 2 ,3, 4
6. Monohydroxybutenyl-mercapturic acid (MHBMA) measured at visits 1, 2 ,3, 4, 7, 10, 13
7. 2-cyanoethylmercapturic acid (CEMA) measured at visits 1, 2 ,3, 4
8. 1-hydroxypyrene (1-OHP) measured at visits 1, 2 ,3, 4
9. 2-hydroxyethylmercapturic acid (HEMA) measured at visits 1, 2 ,3, 4
10. 11-dehydrothromboxane B2 (11-dTX B2) measured at visits 1, 2 ,3, 4, 7, 10, 13
11. 4-hydroxy-nonenal + metabolites (4-HNE) measured at visits 1, 2 ,3, 4, 7, 10, 13
12. Creatinine measured at visits 1, 2 ,3, 4, 7, 10, 13

Measured from blood samples:
1. N-(2-cyanoethyl)valine (HB [haemoglobin] adduct; CEVal) measured at visits 1, 2 ,3, 4, 7, 10, 13
2. White blood cell count (WBC count) measured at visits 1, 2 ,3, 4, 7, 10, 13
3. Monocyte chemotactic protein 1/C-C motif chemokine ligand 2 (MCP 1/CCL2) measured at visits 1, 4, 7, 10, 13
4. Soluble intercellular adhesion molecule-1 (s-ICAM1) measured at visits 1, 4, 7, 10, 13
5. Fibrinogen (Fib) measured at visits 1, 4, 7, 10, 13
6. High-sensitivity C-reactive protein (hsCRP) measured at visits 1, 4, 7, 10, 13
7. Homocysteine (HMCys) measured at visits 1, 4, 7, 10, 13
8. Glucose (Gluc) measured at visits 1, 4, 7, 10, 13
9. Plasminogen activator inhibitor-1 (PAI-1) measured at visits 1, 4, 7, 10, 13
10. Tissue plasminogen activator (tPA) measured at visits 1, 4, 7, 10, 13
11. E-Selectin (SELE) measured at visits 1, 4, 7, 10, 13
12. Endothelin-1 (ET-1) measured at visits 1, 4, 7, 10, 13
13. 3-nitrotyrosine (3-NTyr) measured at visits 1, 4, 7, 10, 13
14. Serum lipids (high-density lipoprotein [HDL], low-density lipoprotein [LDL], total cholesterol [CholTotal], triglycerides [Trigly]) measured at visits 1, 2 ,3, 4, 7, 10, 13

Measured from exhaled breath:
1. Nitric oxide (NO) measured at visits 1, 2 ,3, 4, 7, 10, 13
2. Carbon monoxide (CO) measured at screening, visits 1, 2 ,3, 4, 7, 10, 13

Physiological measures:
1. Blood pressure at screening, visits 1, 2 ,3, 4, 7, 10, 13
2. Spirometry at screening, visits 1, 2 ,3, 4, 7, 10, 13:
2.1. Peak flow
2.2. Forced vital capacity (FVC)
2.3. Forced expiratory flow (FEF) 25-75%
2.4. Forced expiratory volume in 1 second (FEV1)
3. Body weight/waist circumference at visits 1, 4, 7, 10, 13
4. Carotid/femoral pulse wave velocity at visits 1, 2 ,3, 4, 7, 10, 13
5. 6-minute walking test at visits 1, 2 ,3, 4, 7, 10, 13
6. Finger plethysmography at visits 1, 4, 7, 10, 13

Questionnaires:
1. Fagerström Test for Cigarette Dependence (FTCD) at screening and at visits 1, 4, 7, 10, 13

2. Product satisfaction at visits 1, 4, 7, 10, 13
3. Smoking cessation quality of life at visits 1, 4, 7, 10, 13
4. Self-reported product usage (eDiary/SMS) recorded throughout the study
5. Cough and Shortness of Breath VAS at visits 1, 4, 7, 10, 13

Safety:
1. Physical examination at screening and at visits 1 to 13 and follow-up
2. Vital signs at screening and at visits 1, 4, 7, 10, 13 and follow-up
3. Electrocardiogram (ECG) at screening and at visits 1, 4, 7, 10, 13 and follow-up
4. Clinical laboratory evaluations at screening and at visits 1, 4, 7, 10, 13 and follow-up
5. Lung function tests at screening, visits 1, 2 ,3, 4, 7, 10, 13
6. Adverse events (AE)/serious adverse events (SAE) recorded throughout the study

Completion date
31/03/2020

Eligibility

Key inclusion criteria
Current inclusion criteria as of 05/03/2019:
1. Males or non-pregnant, non-lactating females, between 23 and 55 years of age, inclusive. Age verification will be performed by checking government issued identification (e.g. passport or driving licence) during Screening
2. Body mass index (BMI) between 17.6 and 32.0 kg/m2, inclusive, body weight exceeding 50 kg (males) or 40 kg (females)
3. Subjects will be in good health, as judged by the Investigator or their appropriately qualified designee based on: medical history, physical examination, vital signs assessment (blood pressure <140 mmHg systolic),12-lead ECG, clinical laboratory evaluations, lung function tests (Gold stage 1 is acceptable; see exclusion criterion 16).
4. Subjects will have given their written informed consent to participate in the study and will have agreed to abide by the study restrictions
5. Subjects must demonstrate the ability to comprehend the Informed Consent Form (ICF), be able to communicate well with the Investigator or their appropriately qualified designee, understand and comply with the requirements of the study, and be judged suitable for the study in the opinion of the Investigator or their appropriately qualified designee
6. Subjects will be willing to refrain from consuming alcohol within 24 hours prior to Screening and Check-in at each study visit, with the exception of the Follow-up Visit
7. Subjects will be willing to refrain from consuming barbequed or chargrilled food, and avoid being in the presence of barbequed or chargrilled food for 48 hours prior to Check-in at each study visit. Subjects will also be willing to avoid food containing poppy seeds for 3 days before both Screening and Check-in at each study visit

Arms A, B and D:
8. Subjects will be regular smokers of commercially manufactured filter cigarettes and/or roll your own cigarettes.
9. Subjects will have smoked for at least five consecutive years prior to Screening
10. Subjects will typically smoke at least 10 and a maximum of 30 CPD and must have a urine cotinine level > 200 ng/mL and an exhaled breath CO level ≥ 7 ppm at Screening
11. Subjects in Arm A who continue to smoke will be willing to use factory-manufactured non-mentholated cigarettes and/or roll your own cigarettes.
12. Subjects in Arms B will be willing to use the study product (THP) provided to them during the

study
13. Subjects in Arm D will be willing to abstain from smoking and using NGPs

Arm E:
14. Subjects will have never smoked (<100 cigarettes in their life and none within 30 days prior to Screening) and will continue to not smoke or use any form of tobacco or nicotine-containing product (including THPs) for the duration of the study.

Previous inclusion criteria:

1. Males or non-pregnant, non-lactating females, between 23 and 55 years of age, inclusive
2. Body mass index (BMI) between 17.6 and 32.0 kg/m2, inclusive, body weight exceeding 50 kg (males) or 40 kg (females)
3. Subjects will be in good health, as judged by the Investigator or their appropriately qualified designee based on: medical history, physical examination, vital signs assessment (blood pressure <140 mmHg systolic),12-lead ECG, clinical laboratory evaluations, lung function tests
4. Subjects will have given their written informed consent to participate in the study and will have agreed to abide by the study restrictions
5. Subjects must demonstrate the ability to comprehend the Informed Consent Form (ICF), be able to communicate well with the Investigator or their appropriately qualified designee, understand and comply with the requirements of the study, and be judged suitable for the study in the opinion of the Investigator or their appropriately qualified designee
6. Subjects will be willing to refrain from consuming alcohol within 72 hours prior to Screening and Check-in at each study visit, with the exception of the Follow-up Visit
7. Subjects will be willing to refrain from consuming cruciferous vegetables and grilled, smoked, fried or barbequed food, and avoid being in the presence of the cooking of cruciferous vegetables, and grilled, smoked, fried or barbequed food for 48 hours prior to Check-in at each study visit. Subjects will also be willing to avoid food containing poppy seeds for 3 days before both Screening and Check-in at each study visit

Arms A to D:
8. Subjects will be regular smokers of commercially manufactured filter cigarettes
9. Subjects will have smoked for at least five consecutive years prior to Screening
10. Subjects will typically smoke at least 10 and a maximum of 30 CPD and must have a urine cotinine level > 200 ng/mL and an exhaled breath CO level > 10 ppm at Screening
11. Subjects in Arm A who continue to smoke will be willing to use factory-manufactured non-mentholated cigarettes
12. Subjects in Arms B and C will be willing to use the study products (THP) provided to them during the study
13. Subjects in Arm D will be willing to abstain from smoking and using NGPs

Arm E:
14. Subjects will have never smoked (<100 cigarettes in their life and none within 30 days prior to Screening) and will continue to not smoke or use any form of tobacco or nicotine-containing product (including THPs) for the duration of the study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
506

Key exclusion criteria
Current exclusion criteria as of 05/03/2019:

1. Male subjects who do not agree, or whose partners of childbearing potential do not agree, to use a barrier method of contraception (i.e. a condom with spermicide) or to refrain from donating sperm from Visit 1 until the end of the Follow-up Visit
2. Female subjects of childbearing potential who do not agree to use a highly effective method of birth control in conjunction with male barrier method contraception (i.e. a condom with spermicide) from the time of signing the ICF until the end of the Follow-up Visit
3. Female subjects who are pregnant or breastfeeding. This will be confirmed at Screening and Visit 1. Any female subject who becomes pregnant during this study will be withdrawn
4. Subjects who have donated: ≥400 mL of blood within 12 weeks (male) or 16 weeks (female) prior to Visit 1, plasma in the 2 weeks prior to Visit 1, platelets in the 6 weeks prior to Visit 1
5. Subjects who have an acute illness (e.g. upper respiratory tract infection) requiring treatment within 4 weeks prior to Visit 1 (subjects who had viral infections that resolved ≥2 weeks prior to Visit 1 will be admissible to this study)
6. Subjects who have a significant history of alcoholism or drug/chemical abuse within 24 months prior to Screening, as determined by the Investigator
7. Subjects who have a positive urine drugs of abuse screen (confirmed by repeat) at Screening or Visit 1 or a positive alcohol breath test (confirmed by repeat) at Screening or Visit 1
8. Subjects who are carriers of the hepatitis B surface antigen (HBsAg), hepatitis C antibody or have a positive result for the test for human immunodeficiency virus (HIV) antibodies
9. 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 Visit 1
10. Subjects who have received any medications or substances (other than tobacco) which interfere with the cyclooxygenase pathway (e.g. anti-inflammatory drugs including aspirin and ibuprofen) within 14 days prior to Visit 1, 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 Visit 1
11. Subjects who perform strenuous physical activity (exceeding the subject's normal activity levels) within 7 days prior to Screening or Visit 1
12. Subjects who are unable to communicate effectively with the Investigator/study staff (i.e. language problem, poor mental development, or impaired cerebral function)
13. Subjects who are unwilling or unable to comply with the study restrictions and requirements
14. Employees and immediate relatives of the tobacco industry and the clinical site
15. Subjects who are still participating in another clinical study (e.g. attending follow-up visits) or who have participated in a clinical study involving administration of an investigational drug (new chemical entity) in the past 3 months prior to first product use
16. Subjects who have any clinically relevant abnormal findings on the physical examination, medical history, ECG, lung function tests (post-bronchodilator FEV1/FVC < 0.7 and FEV1 < 80% predicted value at post-bronchodilator spirometry or have an asthma condition [post-

bronchodilator FEV1/FVC < 0.75 and reversibility in FEV1R > 12% and > 200 mL from pre- to post-bronchodilator values at Screening]) or clinical laboratory panel, unless deemed not clinically significant by the Investigator or their appropriately qualified designee
17. Subjects who have, or who have a history of, any clinically significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological or other major disorder that, in the opinion of the Investigator or their appropriately qualified designee, would jeopardise the safety of the subject or impact on the validity of the study results
18. Subjects who have previously been diagnosed with any form of malignancy
19. Subjects who have any clinically significant abnormal laboratory safety findings at Screening, as determined by the Investigator or their appropriately qualified designee (1 repeat assessment is acceptable)
20. Subjects who have previously been enrolled in or withdrawn from this study
21. Subjects who, in the opinion of the Investigator, should not participate in this study

Arms A, B and D:
22. Subjects who regularly use any nicotine or tobacco product other than commercially manufactured filter cigarettes and/or roll your own cigarettes within 14 days of Screening

Arms A and B:
23. Subjects who are self-reported non-inhalers (smokers who draw smoke from the cigarette into the mouth and throat but who do not inhale)
24. Subjects who, prior to randomisation, are planning to quit smoking in the next 12 months. All subjects will be informed that they are free to quit smoking and withdraw from the study at any time. Any subject who decides to quit smoking will be directed to appropriate stop smoking services.

Previous exclusion criteria:

1. Male subjects who do not agree, or whose partners of childbearing potential do not agree, to use a barrier method of contraception (i.e. a condom with spermicide) in addition to a second highly effective method of contraception used by their female partners or to refrain from donating sperm from Visit 1 until the end of the Follow-up Visit
2. Female subjects of childbearing potential who do not agree to use a highly effective method of birth control in conjunction with male barrier method contraception (i.e. a condom with spermicide) from the time of signing the ICF until the end of the Follow-up Visit
3. Female subjects who are pregnant or breastfeeding. This will be confirmed at Screening and Visit 1. Any female subject who becomes pregnant during this study will be withdrawn
4. Subjects who have donated: ≥400 mL of blood within 12 weeks (male) or 16 weeks (female) prior to Visit 1, plasma in the 2 weeks prior to Visit 1, platelets in the 6 weeks prior to Visit 1
5. Subjects who have an acute illness (e.g. upper respiratory tract infection) requiring treatment within 4 weeks prior to Visit 1 (subjects who had viral infections that resolved ≥2 weeks prior to Visit 1 will be admissible to this study)
6. Subjects who have a significant history of alcoholism or drug/chemical abuse within 24 months prior to Screening, as determined by the Investigator
7. Subjects who have a positive urine drugs of abuse screen (confirmed by repeat) at Screening or Visit 1 and a positive alcohol breath test (confirmed by repeat) at Screening or Visit 1
8. Subjects who are carriers of the hepatitis B surface antigen (HBsAg), hepatitis C antibody and have a positive result for the test for human immunodeficiency virus (HIV) antibodies
9. 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 Visit 1

10. Subjects who have received any medications or substances (other than tobacco) which interfere with the cyclooxygenase pathway (e.g. anti-inflammatory drugs including aspirin and ibuprofen) within 14 days prior to Visit 1, 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 Visit 1
11. Subjects who perform strenuous physical activity (exceeding the subject's normal activity levels) within 7 days prior to Screening or Visit 1
12. Subjects who are unable to communicate effectively with the Investigator/study staff (i.e. language problem, poor mental development, or impaired cerebral function)
13. Subjects who are unwilling or unable to comply with the study restrictions and requirements
14. Employees and immediate relatives of the tobacco industry and the clinical site
15. Subjects who are still participating in another clinical study (e.g. attending follow-up visits) or who have participated in a clinical study involving administration of an investigational drug (new chemical entity) in the past 3 months prior to first product use
16. Subjects who have any clinically relevant abnormal findings on the physical examination, medical history, ECG, lung function tests (post-bronchodilator FEV1/FVC < 0.7 and FEV1 < 80% predicted value at post-bronchodilator spirometry or have an asthma condition [post-bronchodilator FEV1/FVC < 0.75 and reversibility in FEV1R > 12% and > 200 mL from pre- to post-bronchodilator values at Screening]) or clinical laboratory panel, unless deemed not clinically significant by the Investigator or their appropriately qualified designee
17. Subjects who have, or who have a history of, any clinically significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, haematological or other major disorder that, in the opinion of the Investigator or their appropriately qualified designee, would jeopardise the safety of the subject or impact on the validity of the study results
18. Subjects who have previously been diagnosed with any form of malignancy
19. Subjects who have any clinically significant abnormal laboratory safety findings at Screening, as determined by the Investigator or their appropriately qualified designee (1 repeat assessment is acceptable)
20. Subjects who have previously been enrolled in or withdrawn from this study
21. Subjects who, in the opinion of the Investigator, should not participate in this study

Arms A to D:
22. Subjects who regularly use any nicotine or tobacco product other than commercially manufactured filter cigarettes within 14 days of Screening

Arms A to C:
23. Subjects who are self-reported non-inhalers (smokers who draw smoke from the cigarette into the mouth and throat but who do not inhale)
24. Subjects who, prior to randomisation, are planning to quit smoking in the next 12 months. All subjects will be informed that they are free to quit smoking and withdraw from the study at any time. Any subject who decides to quit smoking will be directed to appropriate stop smoking services

Date of first enrolment
15/02/2018

Date of final enrolment
31/03/2019

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Wales

Study participating centre
Covance Clinical Research Unit Ltd
Springfield House
Hyde Street
Leeds
United Kingdom
LS2 9LH

Study participating centre
SIMBEC Research Ltd
Simbec House
Merthyr Tydfil Industrial Park
Pentrebach
Merthyr Tydfil
United Kingdom
CF48 4DR

Study participating centre
Celerion (GB) Ltd
22-24 Lisburn Road
Belfast
United Kingdom
BT9 6AD

Study participating centre
Richmond Pharmacology Ltd
1a Newcomen Street
London Bridge
London
United Kingdom
SE1 1YR

Sponsor information

Organisation
British American Tobacco (Investments) Ltd

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
Participant level data will be available upon request. Deidentified study data including all data captured using the eCRF, subject diaries and full bioanalytical reports available in SDTM format. 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. Data requestors will need to sign a data access agreement. Data will be available for at least 5 years following publication.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	three-month results	16/02/2021	15/04/2021	Yes	No

Results article	six-month results	01/07/2021	15/07/2021	Yes	No
Results article		28/08/2022	01/09/2022	Yes	No
Protocol article	protocol	01/09/2019	07/05/2019	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Statistical Analysis Plan	statistical analysis plan	28/01/2020	19/05/2020	No	No