ISRCTN80651909 https://doi.org/10.1186/ISRCTN80651909

A study to examine changes in exposure to cigarette smoke chemicals when a smoker switches to using a tobacco heating product or an e-cigarette

Submission date
22/02/2017

Recruitment status
No longer recruiting

Registration date
09/03/2017

Overall study status
Completed

Last Edited
25/05/2021

Condition category
Other

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

Plain English summary of protocol

Background and study aims

Smoking is a leading cause of numerous diseases including lung cancer, chronic obstructive pulmonary (lung) disease, and atherosclerotic cardiovascular (heart) disease. Reducing the negative health impacts of smoking is a clear public health priority and has led to a series of initiatives to persuade people not to smoke. Despite these efforts, smoking rates in adult populations worldwide remain at 15%-25%. Cigarette smoke is a mixture of more than 5,600 identified chemicals and some of these chemicals contribute to the harmful effects of smoking. Exposure to them can be tested by measuring the levels of these chemicals in urine. Nicotine, a chemical found naturally in tobacco leaf and which transfers into cigarette smoke, is mainly responsible for the addictive properties of cigarette smoking. However, it is not the nicotine but many of the other chemicals that are thought to be responsible for the harmful effects of smoking. Although many smokers attempt to quit smoking, few succeed without help. Nicotine replacement therapy (NRT), first introduced in 1978, replaces the nicotine from cigarettes and is thought to assist subjects in stopping smoking by reducing cravings, symptoms of withdrawal and mood changes. Examples of NRT include nicotine patches, gums and, more recently, sprays. In general, the delivery of nicotine from NRT products does not closely match that of cigarettes and this might explain the relatively poor effectiveness of NRT products as aids to quitting smoking. Next Generation Products (NGPs) are nicotine-delivering devices that can be broadly categorized as either tobacco heating products (THPs) or electronic inhalable vapour products (e-cigarettes). THPs are electronic devices that heat tobacco, typically to temperatures lower than 350°C, rather than combusting it. Due to this lack of combustion, far fewer chemicals are formed but nicotine is still released and can be inhaled. THP consumables look similar to a cigarette, including a filter section at the mouth end of the tobacco stick. Less is known about the properties of THPs compared to e-cigarettes. However, a study of the chemicals found in the vapour from a THP when tested on a smoking machine revealed significant reductions in the levels of many chemicals when compared to those found in cigarette smoke. The THP vapour has also been found to contain significant levels of nicotine. E-cigarettes are small, battery-powered devices that heat a liquid containing nicotine to produce a vapour that can be inhaled by the

user. As there is no combustion (similar to THPs), and also because the liquid does not contain tobacco, far fewer chemicals are found in e-cigarette vapour compared to cigarette smoke. Studies have shown that e-cigarettes deliver significant amounts of nicotine to users. However, since measurements of other chemicals in e-cigarette vapour show that they are either absent or present at very low levels compared to those found in cigarette smoke, it is expected that there should be much less exposure to those chemicals in e-cigarette users. The aim of this study is to examine the exposure to cigarette smoke chemicals in smokers who switch from conventional cigarettes to either THPs or e-cigarettes.

Who can participate?
People aged between 21 and 55 who smoke 10 to 30 cigarettes per day

What does the study involve?
The study involves staying in a research clinic for a period of up to 8 days. For the first two days, participants continue to smoke cigarettes and their urine is collected to measure the levels of chemicals. Daily samples of blood and breath are also collected for tests. For the following 5 days participants are randomly allocated to either continue smoking cigarettes, switch to using a THP (either a commercially available THP or a new THP that is being developed) or a developmental e-cigarette, or quit using any tobacco products. Urine and blood/breath samples are also collected during this time. Participants in the tobacco use groups then stay in the clinic for a further day so blood samples can be taken to test for nicotine levels when they use a single tobacco product under controlled conditions.

What are the possible benefits and risks of participating?
Benefits include being involved in research assessing whether tobacco heating products or e-cigarettes may reduce the impact of tobacco use on a smoker and having access to smoking cessation advice. Participants also receive a medical assessment before entering the study, which may help them to understand more about certain aspects of their general health. The incremental risks for subjects participating in the study who would otherwise continue to smoke regularly are considered to be minor. These include the risk of side effects from nicotine and tobacco use, although since participants will already be using tobacco products the risks related to the side effects of nicotine from use of the study products are low. Other risks include discomfort or minor pain from the methods used to collect blood samples, as well as a low risk of infection, bruising or bleeding at the blood collection site.

Where is the study run from?
Celerion Clinic (UK)

When is the study starting and how long is it expected to run for?
August 2016 to October 2017

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

Who is the main contact?
Dr Michael McEwan
mike_mcewan@bat.com

Contact information

Type(s)

Scientific

Contact name
Dr Michael McEwan

ORCID ID
https://orcid.org/0000-0001-5561-4438

Contact details
British American Tobacco (Investments) Ltd
R&D Centre
Regents Park Road
Southampton
United Kingdom
SO15 8TL
+44 (0)2380 588855
mike_mcewan@bat.com

Additional identifiers

Protocol serial number
BAT3116007

Study information

Scientific Title
A randomised controlled single-centre open-label study in healthy subjects to evaluate the effect on biomarkers of exposure of switching from a combustible cigarette to a Next Generation Product (NGP)

Study objectives
There will be significant reductions in biomarkers of exposure to cigarette smoke toxicants in smokers who switch from smoking conventional cigarettes to using tobacco heating products or e-cigarettes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Health and Social Care Research Ethics Committee A (HSC REC A) of The Office for Research Ethics Committees Northern Ireland (ORECNI), 02/05/2017, ref: 17/NI/0065

Study design
Single-centre randomised longitudinal controlled interventional study

Primary study design
Interventional

Study type(s)
Other

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

Interventions
Participants will be randomised either to:
1. Remain smoking a conventional (control) cigarette for 5 days
2. Switch to using a developmental tobacco heating product for 5 days
3. Switch to using a developmental e-cigarette for 5 days
4. Switch to using a commercially-available tobacco heating product for 5 days
5. Cease the use of any tobacco products for 5 days
The randomization will be computer-generated using SAS Version 9.3.

After entering the clinic, subjects will smoke regular cigarettes ad libitum but up to a maximum amount of 120% of their usual daily cigarette consumption, for a baseline period of 2 days. After this period and according to the randomisation, subjects will either remain smoking for the next 5 days or will switch to using a tobacco heating product/e-cigarette or refrain from using any tobacco products, also for 5 days. After this period, subjects in all the tobacco/e-cigarette-use groups will remain in the clinic for a further day for a single-use nicotine pharmacokinetic sampling period. After the study, subjects will be followed-up after a period of 5-7 days.

Intervention Type
Behavioural

Primary outcome(s)
1. Within-group changes in urinary biomarkers of exposure to cigarette smoke toxicants (TNeq, total NNAL, total NNN, 3-HPMA, HMPMA, S-PMA, MHBMA, CEMA, 4-ABP, o-Tol, 2-AN, 1-OHP, HEMA, AAMA and GAMA), measured in daily 24h urine collections on 1 baseline day (Day 2) and 3 product use days (Days 3, 5 and 7)
2. Within-group changes in exhaled breath CO (measured daily in exhaled breath using a CO meter), urinary 8-Epi-PGF2α Type III (measured daily from a urine sample) and white blood cell count (performed on a sample of venous blood collected using direct venipuncture on Days 2, 5 and 7)

Key secondary outcome(s))
1. Between-group differences in urinary biomarkers of exposure to cigarette smoke toxicants (TNeq, total NNAL, total NNN, 3-HPMA, HMPMA, S-PMA, MHBMA, CEMA, 4-ABP, o-Tol, 2-AN, 1-OHP, HEMA, AAMA and GAMA), measured in daily 24h urine collections on 1 baseline day (Day 2) and 3 product use days (Days 3, 5 and 7)
2. Between-group differences in exhaled breath CO (measured daily in exhaled breath using a CO meter), urinary 8-Epi-PGF2α Type III (measured daily from a urine sample) and white blood cell count (performed on a sample of venous blood collected using direct venipuncture on Days 2, 5 and 7)
3. Plasma nicotine pharmacokinetic parameters (Tmax, Cmax and AUC0-tlast), measured in venous blood samples taken at -5, 1, 3, 4, 5, 6, 7, 10, 15, 30, 60, 120, and 240 minutes relative to the first puff on a single cigarette/THP consumable
4. Subjects' satisfaction with the study products, assessed using a single-item questionnaire at the end of all study procedures
5. Safety profile, assessed at the end of the study period by examining adverse event record and also by vital signs, physical examination, ECG, lung function test, blood and urine tests and a pregnancy test (female subjects only)

Completion date
03/10/2017

Eligibility

Key inclusion criteria
1. Males or females aged between 21 and 55 years of age, inclusive
2. Body mass index (BMI) of 18.5 to 30.0 kg/m2, inclusive; a body weight exceeding 52 kg (males) or 45 kg (females)
3. In good health, as judged by the PI or the appropriately qualified designee based on medical history, physical examination, vital signs assessment, 12-lead ECG, clinical laboratory evaluations, and 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 PI or the appropriately qualified designee, understand and comply with the requirements of the study, and be judged suitable for the study in the opinion of the PI or the appropriately qualified designee
6. Willing to refrain from consuming alcohol within 72 hours prior to Admission
7. Willing to refrain from consuming cruciferous vegetables, and grilled, fried or barbequed food, and avoid being in the presence of the cooking of cruciferous vegetables, and grilled, fried or barbequed food for 48 hours prior to Admission
8. Subjects will be regular smokers of factory made, non-menthol cigarettes whose chosen brand is within the ISO tar bands 6 mg to 10 mg, inclusive
9. Subjects will have smoked their chosen brand for a minimum of 6 months and will have smoked for at least 3 years prior to Screening
10. Subjects will typically smoke 10 to 30 cigarettes per day, inclusive, and must have a urine cotinine level >200 ng/mL at Screening
11. Subjects will be willing to use the study products (comparator cigarette or THP product or e-cigarette) and use only the products provided to them during clinical confinement, or to abstain from smoking if assigned to the cessation arm

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
148

Key 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 Admission (Day -1) until 5 days after Discharge
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 5 days after Discharge
3. 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
4. Subjects who have donated ≥400 mL of blood within 90 days prior to Admission, plasma in the 7 days prior to Admission, or platelets in the 6 weeks prior to Admission
5. Subjects who have an acute illness (e.g. upper respiratory tract infection. viral infection, etc.) requiring treatment within 4 weeks prior to Admission
6. Subjects who have used any nicotine or tobacco product other than commercially manufactured non-menthol, filter cigarettes within 14 days of Screening
7. Subjects who are self-reported non-inhalers (smokers who draw smoke from the cigarette 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
8. Subjects who, prior to enrolment, 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
9. Subjects who have a significant history of alcoholism or drug/chemical abuse within 24 months prior to Screening, as determined by the PI or the appropriately qualified designee.
10. Subjects who have a positive urine drugs of abuse and alcohol screen (confirmed by repeat) at Screening or Admission or a positive alcohol breath test (confirmed by repeat) at Screening or Admission
11. Subjects who have serum hepatitis, are carriers of the hepatitis B surface antigen (HBsAg), are carriers of the hepatitis C antibody, or have a positive result for the test for human immunodeficiency virus (HIV) antibodies
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 Admission
13. 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 or 5 half-lives of the drug (whichever is longer) prior to Admission, or are known to be strong inducers or inhibitors of cytochrome P450 (CYP) enzymes within 14 days prior to Admission
14. Subjects who perform strenuous physical activity (exceeding the subject's normal activity levels) within 7 days prior to Screening or Admission
15. Subjects who are unable to communicate effectively with the PI/study staff (i.e. language problem, poor mental development, or impaired cerebral function)
16. Subjects who are unwilling or unable to comply with the study requirements
17. Employees and immediate relatives of employees, of the tobacco industry, journalism, television and radio reporting, public relations, market research, advertising, and the clinical site
18. 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
19. Subjects who have any clinically relevant abnormal findings on the physical examination, medical history, ECG, lung function tests (forced expiratory volume in 1 second/ forced vital

capacity (FEV1/FVC) >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >80% predicted value), or clinical laboratory panel, unless deemed not clinically significant by the PI or the appropriately qualified designee
20. 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 PI or the appropriately qualified designee, would jeopardise the safety of the subject or impact on the validity of the study results
21. Subjects who have previously been diagnosed with any form of malignancy
22. Subjects who have any clinically significant abnormal laboratory safety findings at Screening and prior to first product use, as determined by the PI or the appropriately qualified designee (1 repeat assessment is acceptable)
23. Subjects who have previously randomized into or withdrawn from this study
24. Subjects who, in the opinion of the PI or the appropriately qualified designee, should not participate in this study

Date of first enrolment
21/04/2017

Date of final enrolment
30/06/2017

Locations

Countries of recruitment
United Kingdom

Northern Ireland

Study participating centre
Celerion
22-24 Lisburn Rd
Belfast
United Kingdom
BT9 6AD

Sponsor information

Organisation
British American Tobacco (Investments) Limited

ROR
https://ror.org/01znsh139

Funder(s)

Funder type
Industry

Funder Name
British American Tobacco (Investments) Limited

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/will be available upon request from Dr Michael McEwan (mike_mcewan@bat.com).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		08/05/2021	25/05/2021	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes