ISRCTN69161830 https://doi.org/10.1186/ISRCTN69161830

A study measuring cannabidiol uptake to the bloodstream from novel cannabidiol-containing food products

Submission date 07/09/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 07/09/2023	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 01/11/2023	**Condition category** Other	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cannabidiol (also known as CBD) is a compound found in the cannabis plant. This study will compare three product forms of cannabidiol: tincture (extract), shot, and chew. The researchers will compare how quickly and to what amount the CBD in the products is absorbed by the body. They will do this by looking at the cannabidiol blood values after product use. In addition, they will look at the breakdown products (metabolites) of cannabidiol in the blood and will ask the participants questions about their experience with the use of the products. They will also investigate how safe the cannabidiol products are and how well they are tolerated when they are given to healthy participants.

Who can participate?
Healthy volunteers aged 19 to 55 years

What does the study involve?
Each participant will be given cannabidiol in three different forms. There are two different types of tincture (extract). These are liquids which will be swallowed. Each product use will consist of two intakes of 1 ml each. There is one shot, which is a drink of 60 ml. There are five types of chew. The chews will be placed in the mouth and chewed for a few minutes. For each chew product participants will have to consume two 4 g pieces. Participants will receive all study products, so eight in total. The order in which participants will receive them will be determined by drawing lots.
The total amount of cannabidiol that will be given each time is 60 mg. At the start of the study, participants will receive training on how to use the tincture (extract) product form and will also get training to become familiar with the questionnaires. Participants will be given a study product on days 3, 5, 7, 9, 11, 13, 15, and 17 of the study. About 7 days after the last study product use, the researchers will call participants for the follow-up phone call. During the follow-up phone call, they will ask participants questions about their wellbeing and if there are any special details about their health. The researchers will also ask questions about their medication use.

What are the possible benefits and risks of participating?
Participants will not benefit from involvement in this study. However, their participation will help the investigators to increase their knowledge about the effects of cannabidiol and to achieve the study objectives. Cannabidiol has already been administered to humans before and it has been extensively tested in the laboratory and on animals. It has been administered before to humans through different routes such as by mouth, on the skin, under the tongue, and in the nose.

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

Who is funding the study?
Organigram Inc. (Canada)

Who is the main contact?
1. Linsey E Haswell, Linsey_Haswell@bat.com
2. Dr Maria Velinova

Contact information

Type(s)
Scientific

Contact name
Miss Linsey Haswell

ORCID ID
https://orcid.org/0000-0002-5663-8834

Contact details
Scientist II Clinical Research
British American Tobacco (Investments) Limited
R&D Centre
Regents Park Road
Southampton
United Kingdom
SO15 8TL
+44 (0)7878881232
Linsey_Haswell@bat.com

Type(s)
Principal investigator

Contact name
Dr Maria Velinova

Contact details
Van Swietenlaan 6
Groningen
United Kingdom
9728 NZ

+31 (0)800 0292044
EDS-NLReceptionGRQM@iconplc.com

Additional identifiers

Protocol serial number
BAT82123038

Study information

Scientific Title
A randomised, controlled, single-centre, open-label study to assess the pharmacokinetics of cannabidiol in tincture, shot and chew products in healthy adult subjects

Study objectives
Cannabidiol (CBD) delivery system will affect the bioavailability of CBD

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 09/10/2023, MREC of the foundation BEBO (Assessment Ethics Biomedical Research) (Dr. Nassaulaan 10, Assen, 9401 HK, Netherlands; +31 (0)592-405871; info@stbebo.nl), ref: NL84918.056.23

Primary study design
Interventional

Study design
Single-centre randomized open-label pharmacokinetic crossover study

Study type(s)
Other

Health condition(s) or problem(s) studied
CBD uptake in healthy adult subjects

Interventions
Prototype tincture_ RTO00075 – 60 mg CBD
Prototype tincture_ RTO00076 - 60 mg CBD
Prototype shot_ RTO00077 - 60 mg CBD
Prototype chew_ RTO00078 - 60 mg CBD
Prototype chew_ RTO00079 - 60 mg CBD
Prototype chew_ RTO00080 - 60 mg CBD
Prototype chew_ RTO00081 - 60 mg CBD
Prototype chew_ RTO00082 - 60 mg CBD

Each participant will be given cannabidiol in three different forms. There are two different types of tincture (extract). These are liquids which will be swallowed. Each product use will consist of two intakes of 1 ml each. There is one shot, which is a drink of 60 ml. There are five types of

chew. The chews will be placed in the mouth and chewed for a few minutes. For each chew product participants will have to consume two 4 g pieces. Participants will receive all study products, so eight in total. The order in which participants will receive them will be determined by drawing lots.

The total amount of cannabidiol that will be given each time is 60 mg. At the start of the study, participants will receive training on how to use the tincture (extract) product form and will also get training to become familiar with the questionnaires. Participants will be given a study product on days 3, 5, 7, 9, 11, 13, 15, and 17 of the study. About 7 days after the last study product use, the researchers will call participants for the follow-up phone call. During the follow-up phone call, they will ask participants questions about their wellbeing and if there are any special details about their health. The researchers will also ask questions about their medication use.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
CBD

Primary outcome(s)
Maximum plasma CBD and 7-OH-CBD concentration (Cmax) and area under the plasma concentration versus time curve 0 to 24 hours (AUC 0-24 hrs), measured by LC-MS/MS after collection of blood samples at pre-use, 0,15, 30 minutes, 1, 1.5, 2, 2.5, 3.5, 4, 4.5, 6, 12 and 24 hours

Key secondary outcome(s)
1. Maximum plasma CBD and 7-OH-CBD time to Cmax (Tmax) 0 to 24 hours (AUC 0-24 hrs), measured by LC-MS/MS after collection of blood samples at pre-use, 0,15, 30 minutes, 1, 1.5, 2, 2.5, 3.5, 4, 4.5, 6, 12 and 24 hours
2. Maximum plasma 7-COOH-CBD concentration (Cmax), time to Cmax (Tmax) and area under the plasma concentration versus time curve 0 to 24 hours (AUC 0-24 hrs), measured by LC-MS /MS after collection of blood samples at pre-use, 0,15, 30 minutes, 1, 1.5, 2, 2.5, 3.5, 4, 4.5, 6, 12 and 24 hours
3. Baseline differences in product experience measured using a questionnaire at pre-use, 30 minutes, 1, 1.5, 2, 2.5, 3.5, 4, 4.5, 6, 12 and 24 hours
4. Overall product liking measured using a questionnaire at 30 mins, 4 and 24 hours

Completion date
29/12/2023

Eligibility

Key inclusion criteria
1. Subjects will be:
1.1. Males or females.
1.2. 19 to 55 years of age, inclusive, demonstrated by appropriate proof of identification.
1.3. Non-smoker and non-nicotine user who has not smoked or used tobacco/nicotine-containing

products e.g. e-cigarettes, heated tobacco products, nicotine pouches or nicotine replacement therapy in the last month.
2. Subjects will have a:
2.1. Body mass index (BMI) of 18.5 to 32.0 kg/m², inclusive.
2.2. Body weight exceeding 52.0 kg (males) or 45.0 kg (females).
3. Subjects will be in good health, as judged by the PI or an appropriately qualified designee based on:
3.1. Medical history
3.2. Physical examination
3.3. Vital signs assessment
3.4. 12-lead ECG
3.5. clinical laboratory evaluations
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 an 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 an appropriately qualified designee.
6. Subjects will have a urinary cotinine level <200 ng/ml.
7. Subjects will be willing to refrain from consuming alcohol within 24 hours prior to admission.
8. Subjects must be willing to use the study products and use only the products provided to them during clinical confinement, and to abstain from any other CBD product use when instructed.
9. Female subjects must be of non-childbearing potential or must use appropriate contraceptive methods.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
19 Years

Upper age limit
55 Years

Sex
All

Key exclusion criteria
Subjects will be excluded from the study if they meet any of the following criteria at screening and admission, unless otherwise stated:
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) in addition to another highly effective method of contraception used by their female partners or to refrain from donating sperm from admission until the end of the study.

2. Female subjects who are pregnant or breastfeeding. This will be confirmed at Screening and admission.
3. Subjects who have donated:
3.1. ≥400 ml of blood within 90 days prior to admission.
3.2. Plasma within 90 days prior to admission.
3.3. Platelets within 6 weeks prior to admission.
3.4. Bone marrow within the last 6 months prior to admission.
4. Subjects who have an acute illness (e.g., upper respiratory tract infection, viral infection, etc.) requiring treatment within 4 weeks prior to admission.
5. Subjects who smoke or use other types of tobacco/nicotine-containing products in the month prior to screening, as reported at screening.
6. Subjects who self-report they are not able or are unwilling to abstain from caffeine for the duration of confinement without withdrawal symptoms.
7. Presence of braces, partials, dentures, or any dental work that could, in the opinion of the PI, affect the conduct of the study.
8. Presence or history in the last 6 months of a significant form of oral and/or pharyngeal inflammation, oral lesions and/or gum disease or temporomandibular joint dysfunction.
9. Subjects who are unable to chew study products.
10. Subjects who:
10.1. Have a significant history of alcoholism or drug/chemical abuse within 24 months prior to screening, as determined by the PI or an appropriately qualified designee.
10.2. Drink alcohol in excess of 21 units per week for males or 14 units per week for females, with one unit = 150 ml of wine or 360 ml of beer or 45 ml of 45% alcohol
11. Subjects who have a positive urine drugs of abuse or alcohol screen (confirmed by repeat) at screening or admission. Subjects with a positive result for cannabinoids will not be excluded.
12. Subjects who have consumed grapefruit, grapefruit juice, Seville oranges, marmalade, pomelo containing products, within 14 days prior to admission and then throughout the entire study duration.
13. Subjects who:
13.1. Are carriers of the hepatitis B surface antigen (HBsAg)
13.2. Are carriers of the hepatitis C antibody
13.3. Have a positive result for the test for human immunodeficiency virus (HIV) antibodies.
14. Subjects who have received any medications or substances (except for CBD) which are known to be strong inducers or moderate or strong inhibitors of CYP3A4 or CYP2C19 enzymes and/or P gp within 28 days (for inducers, including St. John's Wort) or 14 days (for inhibitors) prior to admission and throughout the study.
15. Subjects who perform strenuous physical activity (exceeding the subject's normal activity levels) within 7 days prior to screening or admission and who are not willing to abstain from strenuous physical activity while in-house.
16. Subjects who have been on a diet incompatible with the on study diet, in the opinion of the PI or an appropriately qualified designee, within the 30 days prior to start of and throughout the study
17. Subjects who are unable to communicate effectively with the PI/study staff (i.e., language problem, poor mental development, or impaired cerebral function).
18. Subjects who are unable to tolerate or unwilling to use the CBD tincture product during the product familiarisation phase.
19. Subjects who are unwilling or unable to comply with the study requirements.
20. Employees and/or immediate relatives of employees of the cannabis industry or the CRU.
21. Participation in a new chemical entity clinical study or a marketed drug clinical study within the 30 days prior to admission.
22. Subjects who have any clinically relevant abnormal findings on the physical examination, medical history, ECG or clinical laboratory panel at screening or admission, unless deemed not

clinically significant by the PI or an appropriately qualified designee.
23. Subjects who have haemoglobin level below the lower limit of normal at screening.
24. Subjects with any positive responses on the C SSRS at screening.
25. Subjects who have, or who have a history of, any clinically significant neurological, gastrointestinal, renal (including urinary tract infection or nephrolithiasis), hepatic, cardiovascular, psychiatric, depression, anxiety, respiratory, metabolic, endocrine, haematological or other major disorder that, in the opinion of the PI or an appropriately qualified designee, would jeopardise the safety of the subject or impact on the validity of the study results.
26. Subjects who have history or presence of hypersensitivity or idiosyncratic reaction to CBD or related compounds.
27. Subjects who have previously been diagnosed with any form of malignancy.
28. Subjects who have previously been randomised into and/or withdrawn from this study.
29. Subjects who, in the opinion of the PI or an appropriately qualified designee, should not participate in this study.

Date of first enrolment
20/09/2023

Date of final enrolment
26/11/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
ICON – Early Development Services
Van Swietenlaan 6
Groningen
Netherlands
9728 NZ

Sponsor information

Organisation
British American Tobacco (United Kingdom)

ROR
https://ror.org/01znsh139

Funder(s)

Funder type
Industry

Funder Name
Organigram Inc

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Linsey Haswell (linsey_haswell@bat.com). After completion of the study, other researchers may request access to some of the non-identifiable data generated as part of this study for their own research projects. Only following approval by the sponsor will this data be shared and only providing the researcher can assure the confidentiality and agree to all terms provided by the sponsor.

IPD sharing plan summary
Available on request