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A study to assess the pharmacokinetic of cannabidiol (CBD) following use of vapour, oral pouch, edible and chew CBD Products

Submission date 15/01/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 18/01/2021	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 02/02/2021	**Condition category** Other	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cannabidiol (CBD) is a chemical in the Cannabis sativa plant, also known as marijuana or hemp. Over 80 chemicals, known as cannabinoids, have been identified in the Cannabis sativa plant. Although the precise mechanism of action of CBD is not clearly understood, in certain dosage levels it has shown promise as a therapeutic drug. The most common route of administration is oral ingestion, either via a capsule or dissolved in an oil solution (e.g., olive or sesame oil). Although a number of studies have demonstrated an increase in the availability of CBD in the blood following oral administration (ingestion), it is not clear if this effect can be observed in other routes of absorption, e.g. via the lungs or mouth lining. This study aims to investigate the effects of CBD when administered in various ways.

Who can participate?
Healthy volunteers aged 21 to 55 years who meet the inclusion and exclusion criteria.

What does the study involve?
On Day 1 of each period, subjects will be provided and use the assigned study product according to the randomisation scheme. Blood samples for measurements for blood pressure, heart rate, and body temperature, and continuous physiological measurements will be collected during and following each product use. Subjects will also complete subjective questionnaires (VAMS and product satisfaction) following each product use. Subjects will be discharged after completing all study procedures and a follow up call will be scheduled within 7 days after the last product use.

What are the possible benefits and risks of participating?
Subjects will not receive any health benefits for participating. The most common side effects related to CBD use are tiredness, vomiting, diarrhoea, changes in appetite and weight and headache

Where is the study run from?
Celerion (UK)

When is the study starting and how long is it expected to run for?
November 2020 to March 2022

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

Who is the main contact?
Dr James Ebajemito, james_ebajemito@bat.com

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
BAT5120022/CA31228

Study information

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

Study objectives
Different CBD delivery format and route of administration will affect CBD bioavailability

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/10/2020, Office for Research Ethics Committee Northern Ireland (ORECNI) (Business Services Organisation, Lissue Industrial Estate West, 5 Rathdown Walk, Moira Road, Lisburn, BT28 2RF, UK; +44 (0)28 9536 1400; info.orecni@hscni.net), ref: 20/NI/0114

Study design
Single-centre randomized open-label 6-period 6-way crossover study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please contact clinicalinfo@bat.com to request a patient information sheet.

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

Interventions
Duration of intervention – single ad libitum use of fixed puff over 30 minutes (vapour arm only)

Follow up - within 1 week of discharge from clinic#

Randomisation - This is an open label study. Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomisation identification number at the time of the first study product use on Day 1 of Period 1, different from the screening number, and will receive the corresponding product, according to a randomisation scheme. All subjects (n=36) will receive Arms G, H, and I; half of the subjects (n=18) will also receive Arms A, B, and C, and the other half (n=18) will receive Arms D, E, and F.
The sequences to be used in the randomisation will be ABICHG, BCAGIH, CGBHAI, GHCIBA, HIGACB, IAHBGC, DEIFHG, EFDGIH, FGEHDI, GHFIED, HIGDFE, and IDHEGF.

Dosages –
a) Vuse (Vype) ePod EPOD2.0_SBR_TF189A60 (ad libitum; fasted): 60 mg/ml CBD
b) Vuse (Vype) ePod EPOD2.0_SBR_TF189A60 (ad libitum; fed state): 60 mg/ml CBD

c) Vuse (Vype) ePod EPOD2.0_SBR_TF184N00 (ad libitum; fasted): 0 mg/ml CBD (Placebo)
d) Vuse (Vype) ePod EPOD2.0_SBR_TF189A60 (fixed; fasted): 60 mg/ml CBD
e) Vuse (Vype) ePod EPOD2.0_SBR_TF189A60 (fixed; fed state): 60 mg/ml CBD
f) Vuse (Vype) ePod EPOD2.0_SBR_TF184N00 (fixed; fasted): 0 mg/ml CBD (Placebo)
g) Velo ORAL_ORC_TF057A12 (ad libitum; fed state): 12 mg/pouch CBD
h) Prototype Edible MELT_CV_TF006A30 (ad libitum; fed state): 30 mg/piece CBD
i) Prototype Chew CHEW_MDM_TF028A30 (ad libitum; fed state): 30 mg/piece CBD

Intervention Type
Other

Primary outcome measure
Plasma PK parameters for CBD, 7-OH–CBD, and 7-COOH CBD: Cmax, Tmax, and AUC0-t measured using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method according to applicable local standard operating procedures (SOPs) at 0, 5 min, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24, 32, 48 hrs relative to start of product use.

Secondary outcome measures
1. VAMS scores and derived parameters (Emax and TEmax) assessed using a VAMS questionnaire at 0, 0.5, 1, 2, 4, 8 hours relative to product use
2. Product satisfaction scores assessed using a product satisfaction questionnaire at 5 min, 0.25, 0.5, 4 and 8 hours relative to product use
3. Blood pressure (sphygmomanometer; mmHg) and heart rate (bpm) (Emax and TEmax) at 0, 5 min, 0.5, 1, 2, 4, 6, 8, 12, 24, 32 hrs
4. Body temperature (thermometer; °C) at 0, 5 min, 0.5, 1, 2, 4, and 8 hrs
5. Product use data (including DML, puff number and use count for the vapour product, and MLE for the oral pouch)

Overall study start date
14/10/2020

Completion date
13/03/2022

Eligibility

Key inclusion criteria
1. 21 to 55 years of age, inclusive, demonstrated by appropriate proof of identification
2.1. Body mass index (BMI) of 18.5 to 30.0 kg/m², inclusive.
2.2. body weight exceeding 52 kg (males) or 45 kg (females).
3. 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
3.6. 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 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 be willing to refrain from consuming alcohol within 24 hours prior to admission
7. At Screening, subjects must be current experienced vapers and current daily users of CBD with at least 6 months use history. Product use status will be based on subject self reporting and confirmed with product use history questionnaires at screening
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 one of the contraceptive methods

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Approximately 36 subjects will be randomized to complete with at least 32 subjects.

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 another highly effective method of contraception used by their female partners or to refrain from donating sperm from Admission until at least 90 days after the last product use.
2. 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.
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 currently smoke >5 cigarettes per day (or equivalent for other types of tobacco /nicotine containing products) as reported at Screening.
6. Subjects who are self-reported non-inhalers (vapers who draw smoke/aerosol from the e-cigarette into the mouth and throat but who do not inhale). Subjects who are determined as non-inhalers at Screening will be excluded.
7. Subjects who are planning to quit using CBD products or quit vaping, during the study or postponing a quit attempt in order to participate in the study.
8. Presence of braces, partials, dentures, or any dental work that could, in the opinion of the PI, affect the conduct of the study (including missing molars).
9. Presence or history of significant form of oral and/or pharyngeal inflammation, oral lesions

and/or gum disease or temporomandibular joint dysfunction.
10. Subjects who 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.
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 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 and throughout the study.
15. Subjects who have received any medications or substances (except for CBD and/or nicotine containing products) 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.
16. Subjects who 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.
17. Subjects who perform strenuous physical activity (exceeding the subject's normal activity levels) within 7 days prior to Screening or Admission.
18. Subjects who are lactose intolerant.
19. 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 Day 1 of Period 1 and throughout the study.
20. Subjects who are unable to communicate effectively with the PI/study staff (i.e., language problem, poor mental development, or impaired cerebral function).
21. Subjects who are unable to tolerate or unwilling to use any of the study products during the product familiarisation phase on Day 3 of Period 1.
22. Subjects who are unwilling or unable to comply with the study requirements.
23. Employees and/or immediate relatives of employees of the tobacco industry or the CRU.
24. Participation in a new chemical entity clinical study or a marketed drug clinical study within the 90 days prior to Day 1 of Period 1.
25. Subjects who have any clinically relevant abnormal findings on the physical examination, medical history, ECG, lung function tests, or clinical laboratory panel at Screening or Admission, unless deemed not clinically significant by the PI or an appropriately qualified designee.
26. Subjects who have haemoglobin level below the lower limit of normal at Screening.
27. Subjects with any positive responses on the C SSRS at Screening.
28. Subjects who have been diagnosed with a significant history of urticaria or asthma (childhood asthmas is acceptable).
29. Subjects who have, or who have a history of, any clinically significant neurological, gastrointestinal, renal (including urinary tract infection or nephrolithiasis), hepatic, cardiovascular, psychiatric, 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.
30. Subjects who have history or presence of hypersensitivity or idiosyncratic reaction to CBD or related compounds.
31. Subjects who are allergic to propylene glycol, glycerin, soy, anethole (trans), damascone (beta), geraniol, hexanal, limonene (d-), linalool, 1 p mentene 8 thiol, benzaldehyde, damascenone (beta), geraniol, methyl cinnamate, benzyl alcohol, or vanitrope.

32. Subjects who have previously been diagnosed with any form of malignancy.
33. Subjects who have previously been randomised into and/or withdrawn from this study.
34. Subjects who, in the opinion of the PI or an appropriately qualified designee, should not participate in this study.

Date of first enrolment
04/03/2021

Date of final enrolment
25/03/2021

Locations

Countries of recruitment
Northern Ireland

United Kingdom

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

Sponsor information

Organisation
British American Tobacco (United Kingdom)

Sponsor details
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Sponsor type
Industry

Website
https://www.bat-science.com/

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

Publication and dissemination plan
Full study protocol, statistical analysis plan, informed consent form, clinical study report will be available. Results from this study will be published in peer-reviewed scientific journals.

Intention to publish date
13/09/2022

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No