Pharmacokinetic study of a novel lipid formulation of cannabidiol (CBD)

CBD-Lipid-PK (CLiP) Study

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1. KEY TRIAL CONTACTS

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2. STUDY SYNOPSIS

Trial Title	Pharmacokinetic study of a novel lipid formulation of cannabidiol (CBD)
Short title	CLiP Study
Type of Study	CTIMP Pharmacokinetic study
Trial Design	Single-centre double-blind two-period crossover pharmacokinetic study
Planned Sample Size	14
Participants	Healthy volunteers
Eligibility Criteria	**Inclusion criteria** i. Healthy volunteers. Defined as healthy on the basis of a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine. ii. Age 18-45 iii. Agreeing to fast 15 hours; 10pm-1pm on dosing days iv. Capable of giving informed consent v. Written informed consent from participant **Exclusion criteria** i. Clinically relevant medical history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the participant. ii. Presence of acute or chronic illness or history of chronic illness sufficient to invalidate the volunteer's participation in the trial or make it unnecessarily hazardous. iii. Impaired endocrine, thyroid, hepatic, respiratory or renal function, diabetes mellitus, coronary heart disease, or history of any neurological or mental illness. iv. Surgery or medical condition that might affect absorption of medicines. v. Blood pressure and heart rate in supine position at the screening examination outside the ranges: blood pressure 90–140 mm Hg systolic, 40–90 mm Hg diastolic; heart rate 40–100 beats/min. Repeat measurements are permitted if values are borderline (i.e. values that are within 5 mm Hg for blood pressure or 5 beats/min for heart rate) or if requested by the investigator. Subjects can be included if the repeat value is within range or still borderline but deemed not clinically significant by the investigator. vi. Loss of more than 400 mL blood during the 3 months before the trial, e.g. as a blood donor. vii. Any prescribed medication (apart from contraceptives) viii. Use of any CBD products within six months of IMP administration ix. Use of any over-the-counter medications or health supplements within the past 2 weeks x. BMI <18 or >30.0kg/m^2 xi. History of alcohol or substance misuse disorder xii. Intake of more than 14 units of alcohol weekly. xiii. Smokes more than 10 cigarettes per day xiv. Use of any illicit substances within the last six months of IMP administration xv. Pregnant or breastfeeding xvi. Women of childbearing potential (as defined in CTFG guidelines, see 5.7 Concomitant Medication) not willing to use a highly effective form of contraception (as defined in CTFG guidelines, see section 5.7 Concomitant Medication) during participation in the study or male

	patients not willing to ensure use of a condom during participation in the study. xvii. eGFR≤ 70 mls/min xviii. Any liver function or renal function test abnormality. A repeat is allowed on one occasion for determination of eligibility. xix. Urine drug screen positive for any substances xx. Positive alcohol breath test xxi. Participant in any other clinical trial or experimental drug study in the past 3 months xxii. Known hypersensitivity to CBD and/or SEEK formulation excipients xxiii. Participant is not able to swallow capsules	
Study Drug	Cannabidiol (CBD) [GMP approved source]	
Formulation	Novel lipid formulation (SEEK-CBD) Standard formulation (STD-CBD)	
Dose	1000mg	
Fed/fasting	Fasting	
Route of Administration	Oral	
Treatment Arms	SEEK-CBD then STD-CBD	
	STD-CBD then SEEK-CBD	
Treatment duration	One dose per experimental visit Two experimental visits lasting 48 hours each	
Follow up duration	48 hours per dose/experiment 2 week washout between experiments Final visit 7-14 days after second dosing session	
Planned Trial Duration	4 months	
Primary objective & outcome measure	To assess whether a novel lipid- formulation can improve the bioavailability of oral CBD in the fasting state.	AUC_{inf}
Secondary objectives & outcome measures	To characterise and compare the pharmacokinetic profiles of a novel CBD formulation and a standard formulation	C_{max} T_{max} AUC_{0-48} $t½$

Pharmacokinetic Abbreviations

AUC_t	Area under the plasma concentration-time curve from time zero to time t.

AUC_{inf}	Area under the plasma concentration-time curve from time zero to time infinity.
Bioavailability	The proportion of drug absorbed into the systemic circulation
C_{max}	The maximum serum concentration that a drug achieves
C_{mean}	The mean serum concentration that a drug achieves over a specified period of time
CBD	Cannabidiol
CRF	Clinical Research Facility
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
King's CRF	NIHR Wellcome Kings Clinical Research Facility
KHPCTO	The King's Health Partners Clinical Trials Office
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
SLaM	South London and Maudsley NHS Foundation Trust
T_{max}	The time after administration of a drug that the C_{max} is observed
$T_{½}$	The time taken for the plasma concentration to fall by half its original value

3. BACKGROUND & RATIONALE

Cannabidiol (CBD) has been approved as a treatment for rare childhood epilepsies(1) and could be an effective treatment for psychotic disorders(2), anxiety disorders(3) and addictions(4). It is available as an oral liquid and as standard oral capsules.

The pharmacokinetics of CBD have been described in the review by Millar et al.(5). CBD is highly lipophilic and has poor oral bioavailability (around 5-10% in the fasted state). It also has very high protein binding capability (>97%) reducing the proportion of the drug which may cross the blood-brain barrier and have pharmacological activity in the brain(6). CBD also undergoes extensive first-pass metabolism in the liver by cytochrome P450 enzymes such as CYP3A4 and CYP2C19(7).

If taken with food, the absorption and bioavailability of CBD are much higher(5). In one study, a high-fat breakfast increased maximum plasma concentration (C_{max}) of CBD by 4.9x (90% CI 4.0–5.9) and area under the plasma concentration-time curve (AUC) by 4.2-fold (90% CI 3.6–4.9)(8). Other studies have similar results(9)(10). As a result of this food effect, when prescribing standard formulations of CBD, patients must carefully schedule their medication according to mealtimes. Otherwise, there may be large day-to-day variation in absorption, which will increase the risk of adverse effects or reduced efficacy.

One way to improve the bioavailability and reduce the food effect is by using a lipid encapsulation. Lipids enhance intestinal absorption by forming micelles, lipid molecules arranged in a spherical form in aqueous solutions. Around a third of CBD is absorbed into micelles(11). Once inside enterocytes, lipids are incorporated into chylomicrons, also known as ultra low-density lipoproteins. These are assembled in enterocytes using long-chain triglycerides, phospholipids, cholesterol and lipoproteins(12). Chylomicrons facilitate intestinal lymphatic transport, bypassing the portal vein (and avoiding first-pass metabolism)(13)(14). For most drugs, absorption through the lymphatic system is negligible, however, for highly lipid-soluble drugs such as CBD, passage into the intestinal lymphatic system may represent an alternative route of delivery into the general circulation(13). Preclinical

research using rats found that administering a lipid alongside CBD increased its peak concentration at mesenteric lymph nodes by 6x(15).

A few studies have examined the pharmacokinetics of novel formulations of CBD in humans, though most of these were at very low, sub-therapeutic doses(16). One study using CBD 25mg found that, compared to a medium-chain triglyceride formulation, a 'novel self-emulsifying drug delivery system' increased C_{max} by 4x and AUC by 2-3x(17). Another study using CBD 90mg showed that, compared to a powder formulation, a lipid formulation increased C_{max} by 22x and AUC by 7x (18). Finally, in a pilot study of a lipid formulation of CBD 10mg, the mean AUC was 7x higher compared to a standard formulation(19).

The formulation used in this study uses a range of fats that are designed to facilitate absorption by enterocytes in the ileum. The lipids that are all EU pharmacopoeia approved and have been used in medicinal products before. The effectiveness of the formulation has already been demonstrated with ibuprofen in the proprietary drug Flarin(20).

This study will compare the pharmacokinetics of this novel lipid formulation of CBD with the standard formulation. It will use a dose of 1000mg as this is the dose that is effective in patients with chronic psychotic disorders(2).

Scientific rationale for the choice of CBD dose

There have been two major clinical trials of CBD in patients with schizophrenia. (2)(21) McGuire et al. demonstrated efficacy at a dose of 1000mg/day CBD (Epidiolex in the fed state), while Boggs et al. found no beneficial effect at a lower dose of 600mg/day (in an alternative formulation). However, the current consensus is that these doses were relatively low, and that the optimal dose for treating schizophrenia is higher. Most evidence on the efficacy and safety of CBD is from epilepsy research. In a recent long-term open-label trial in children and adolescents with epilepsy (n=368, mean age 16 years, followed up for 3 years), participants were prescribed doses of CBD up to 30mg/kg/day (Epidiolex in the fed state).(22) After dose titration, the majority of participants were prescribed a daily dose greater than 20mg/kg/day, equivalent to 1400mg/day in a 70kg man. Because that study used Epidiolex in the fed state, the bioavailability is approximately equivalent to that with a 1000mg dose of the novel formulation (which mimics the effect of the fed state) in the study that we propose. In the epilepsy study by Patel et al., 'doses above 20 mg/kg/day had acceptable tolerability, and no new safety issues emerged.'

We have selected a dose of 1000mg/day of the novel (formulation of CBD SEEK-CBD) for the proposed study because we plan to use this dose and formulation in subsequent clinical trials in patients with schizophrenia. This is therefore the appropriate dose for collecting pharmacokinetic data prior to its use in patients. Establishing its bioavailability empirically is particularly important, as CBD does not demonstrate dose-proportionality. (C_{max} slope 0.73; AUC_t slope 0.64).(Taylor et al. 2018)

A 7-fold increase in CBD exposure with 1000mg of SEEK-CBD would be dose equivalent to a 4-5 fold increase in exposure with 1500mg of regular CBD following a meal. In a study by Taylor et al (8), healthy volunteers received a single oral dose of conventional 1500 mg CBD in either the fed (high-fat breakfast) or fasted state. Food increased C_{max} by 4.85-fold (95% CI: 4.01–5.87) and AUC_t by 4.2-fold (90% CI 3.63–4.85). Critically, this study found that 'there was no worsening in the severity of TEAEs in the fed state [compared to the unfed state], hence there is no appreciable safety concern'. Moreover, there were no serious adverse events: the most common were nausea, headache, and somnolence.

Several features of the proposed study's design will ensure the safety of the participants. The drugs will be administered in a state of the art NIHR Clinical Research Facility at King's College Hospital, which is purpose-built for pharmacokinetic studies of novel compounds. Adverse events will be monitored regularly, with medical staff will be on hand at all times. Participants will only leave the facility when all clinical and phsyiological measures are normal, and will be able to contact the investigators at any time after they leave. Participants will be able to remain in hospital overnight if required. The safety blood tests (LFTs, U&Es, FBC) are taken 4 hours post-dosing and the results will be available within 24 hours. If unexpected adverse events do arise, subsequent experimental sessions can be suspended and the study drug dose can be reduced. This contingency has been explicitly incorporated into the protocol (see section 9.5). We have also limited the maximum number of dosing sessions per day to three, so that action can be taken before multiple participants receive the study drug.

The gut microbiome and the endocannabinoid system

Commensal gut bacteria synthetise endocannabinoid precursors and influence the systemic availability of endocannabinoid agonists (e.g., anandamide).(23) This is important as endocannabinoids may mediate CBD's therapeutic effects.(24) This study will therefore complete a novel, exploratory analysis by comparing endocannabinoid levels within the two treatment arms to assess whether they are affected by the gut microbiome (ie. not between arms as the novel CBD should result in increased bioavailability, independent of the microbiome). The gut microbiome can also affect the activity of CYP3A4, a key enzyme involved in the breakdown of CBD.(25)

4. OBJECTIVES AND OUTCOME MEASURES

4.1 Primary objective

To assess whether the novel formulation is able to increase the bioavailability of oral CBD in the fasting state.

Hypothesis: the novel formulation will increase the AUC_{inf} for a single dose of oral CBD in the fasting state.

Primary outcome

Difference in AUC_{inf} for a single dose of oral CBD between the novel and standard formulations in the fasting state.

4.2 Secondary objectives

To characterise and compare the pharmacokinetic profiles of the novel CBD formulation and a standard formulation

Secondary outcomes

Differences between novel and standard formulations for:

i. Maximum plasma concentration (C_{max})
ii. Time after administration of drug when maximum plasma concentration is reached (T_{max})

iii. Plasma half-life (t½)
iv. Area under the concentration-time curve from time zero to 48hours (AUC_{0-48})

4.3 Exploratory objective

To assess the effect of the gut microbiome on endocannabinoid and CBD metabolism. Outcomes are not pre-specified as this is an exploratory analysis.

4.4 TRIAL DESIGN

Single-centre double-blind two-period crossover pharmacokinetic study.

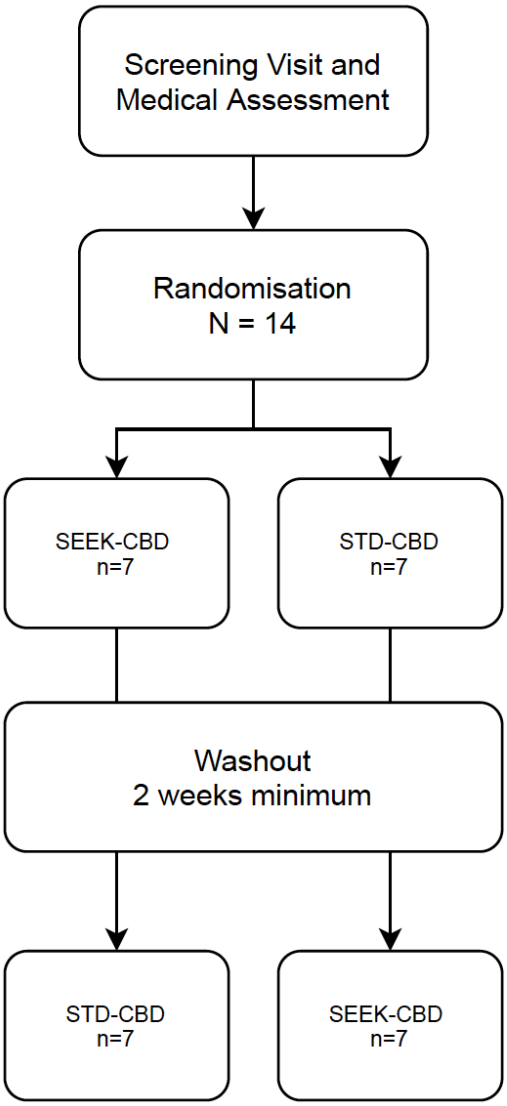
The study includes one baseline screening visit followed by two experimental visits each lasting 48 hours, separated by a minimum 2 weeks washout. Participants will return home each day and will not stay in the hospital overnight.

4.5 Trial Flow Chart

	Screening Visit Day -28 to day 0	Experimental visits 1 & 2*			Follow up visit
		Day 1	Day 2	Day 3	7-14 days after experiment 2 day 1
Consent	X				
Demographic information	X				
Medical Assessment**	X				
Height, weight, body fat	X				
Eligibility Review	X	X			
Urine Pregnancy test	X	X			X
Urine Drug Screen	X	X			
Alcohol breath test	X	X			
Fasting		X			
Drug Administration		X			
Intravenous Cannulation		X			
Blood sampling (FBC, LFTS, U&Es)	X	X			
Blood sampling (CBD and metabolites)		X	X	X	
Urinalysis	X	X			
Vital Signs	X	X	X	X	
Drug Effects Questionnaire (DEQ-5)		X	X	X	
Gastrointestinal Symptom Rating Scale		X	X	X	
Stool Sample Kits	X				
Adverse events		X	X	X	X
Washout period*				X	

*Minimum 2 weeks between experimental visits

**Includes physical exam, vital signs, urine drug screen, alcohol breath test, blood test (U&Es, LFTs, FBC)


Screening Visit and Medical Assessment
Randomisation N = 14
SEEK-CBD n=7
STD-CBD n=7
Washout 2 weeks minimum
STD-CBD n=7
SEEK-CBD n=7

5. TRIAL MEDICATION

5.1 Study Drug

The study drug is cannabidiol, a naturally occurring phytocannabinoid with minimal adverse effects. CBD oral solution is an approved treatment for rare childhood epilepsy syndromes.

The trial will use two formulations of CBD:

1. CBD standard formulation (STD-CBD)
2. CBD novel lipid formulation (SEEK-CBD).

Participants will be administered the same total dose of CBD in both arms (1000mg). Both STD-CBD and SEEK-CBD capsules contain 200mg CBD. Participants will therefore be administered 5x 200mg capsules.

The study drug will be provided by SEEK pharmaceuticals. The trial will use the same source of CBD for both arms.

The two formulations will have an identical appearance so that participants cannot tell which formulation they have been administered.

5.2 Risks, known drug reactions and interaction with other therapies

The risks associated with the study are minimal. CBD has few adverse effects. A meta-analysis of randomized controlled clinical trials found that when prescribed alone, diarrhoea was the only adverse effect (26). CBD also has pharmacokinetic interactions with other medicines via hepatic CYP enzymes, but these are highly unlikely to be relevant to this study as concomitant medications (apart from contraceptives) are prohibited. Previous studies have tested oral doses of CBD (Epidiolex) as high as 4500mg and 6000mg without severe or serious adverse events(8) (27).

The BNF recommends that clinicians should avoid prescribing enzyme-inducing drugs alongside contraceptive medications. CBD is a potent inhibitor of CYP2C19 and CYP3A4 and is not known to have any other clinically relevant enzyme interactions(6).

CBD is not known to cause drug reactions.

5.3 Formulation

SEEK pharmaceuticals will provide both formulations.

The novel SEEK-CBD formulation contains the following excipients:

- Gelucire 43/01 (glycerides only; hard fat [EP]), manufactured by Gattefosse
- Maisine CC (glyceryl monolinoleate), manufactured by Gattefosse
- PEG 400 (polyethylene glycol 400)

Each 200mg CBD capsule contains 400mg Gelucire 43/01, 200mg Maisine CC and 0.008mls PEG 400. The Maisine CC, Gellucire 43/01 and PEG400 are mixed with heating in a closed vessel to 50ºC degrees. CBD is added in a single portion and is stirred at 50ºC for 30 minutes. The mixture is cooled to approximately 40ºC and then filled into the hard gelatin capsules. The top part of the capsule is replaced and the filled capped capsules are left to stand at room temperature until solidified. The capsules are then stored in a plastic bag. All excipients are GMP approved. The materials used in the manufacture of the capsules is of plant origin.

5.4 Drug storage and supply

The investigational product will be purchased from the manufacturer free of charge. It will be stored below 25oC°C in the Maudsley Pharmacy. At the end of the study, any unused study drug will either be returned to the manufacturer or will be destroyed by the Maudsley Pharmacy according to standard local procedures.

5.5 Preparation of Investigational Medicinal Product

The study drug will be manufactured by Eurofins. It will be sent to IPS Pharma who will add the Annex 13 labels. IPS Pharma will complete the final Qualified Person (QP) release. The labels will have been approved by Maudsley Pharmacy. The study drug will dispensed by the Maudsley pharmacy according to standard procedures.

5.6 Dosing, Compliance & Drug Accountability

Participants will be administered a dose of CBD 1000mg on each experimental visit. There will be a minimum of 2 weeks washout between study drug administrations (i.e. between day 1 of each experiment). There is no maximum timeframe between doses. Eligibility for the study will be reassessed on Day 1 of experimental visit 2.

There are not expected to be any issues with either compliance or drug accountability. Full IMP accountability will be maintained. If medication is dispensed by the Maudsley Pharmacy but is not administered (for example, if a participant withdraws from the study during an experimental visit) the drug will be returned to the Maudsley Pharmacy to be disposed of according to standard local procedures.

5.7 Concomitant Medication

Apart from contraceptives, concomitant medications are not permitted during the study and are an exclusion criterion.

There is inadequate information on the effects of cannabidiol on the foetus. Female participants of child-bearing potential* should use a highly effective method of contraception** for the duration of the trial and for 4 weeks after the completion of the trial.

*A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone

(FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal

- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence (abstinence should only be used as a contraceptive method if it is in line with the subjects' usual and preferred lifestyle. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception)

Males participants must be willing to use a condom throughout the duration of the study.

6. SELECTION AND WITHDRAWAL OF PARTICIPANTS

6.1 Inclusion criteria

i. Healthy volunteers. Defined as healthy on the basis of a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine.
ii. Age 18-45
iii. Agreeing to fast 15 hours; 10pm-1pm on dosing days
iv. Capable of giving informed consent
v. Written informed consent from participant

6.2 Exclusion criteria

i. Clinically relevant medical history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the participant.
ii. Presence of acute or chronic illness or history of chronic illness sufficient to invalidate the volunteer's participation in the trial or make it unnecessarily hazardous.
iii. Impaired endocrine, thyroid, hepatic, respiratory or renal function, diabetes mellitus, coronary heart disease, or history of any neurological or mental illness.
iv. Surgery or medical condition that might affect absorption of medicines.
v. Blood pressure and heart rate in supine position at the screening examination outside the ranges: blood pressure 90–140 mm Hg systolic, 40–90 mm Hg diastolic; heart rate 40–100 beats/min. Repeat measurements are permitted if values are borderline (i.e. values that are within 5 mm Hg for blood pressure or 5 beats/min for heart rate) or if requested by the investigator. Subjects can be included if the repeat value is within range or still borderline but deemed not clinically significant by the investigator.
vi. Loss of more than 400 mL blood during the 3 months before the trial, e.g. as a blood donor.
vii. Any prescribed medication (apart from contraceptives)
viii. Use of any CBD products within six months of IMP administration
ix. Use of any over-the-counter medications or health supplements within the past 2 weeks
x. BMI <18 or >30.0kg/m^2
xi. History of alcohol or substance misuse disorder
xii. Intake of more than 14 units of alcohol weekly.
xiii. Smokes more than 10 cigarettes per day
xiv. Use of any illicit substances within the last six months
xv. Pregnant or breastfeeding
xvi. Women of childbearing potential (as defined in CTFG guidelines, see 5.7 Concomitant Medication) not willing to use a highly effective form of contraception (as defined in CTFG guidelines, see section 5.7 Concomitant Medication) during participation in the study or male patients not willing to ensure use of a condom during participation in the study.
xvii. eGFR≤ 70 mls/min
xviii. Any liver function or renal function test abnormality. A repeat is allowed on one occasion for determination of eligibility.
xix. Urine drug screen positive for any substances
xx. Positive alcohol breath test
xxi. Participant in any other clinical trial or experimental drug study in the past 3 months
xxii. Known hypersensitivity to CBD and/or SEEK formulation excipients
xxiii. Participant is not able to swallow capsules

6.3 Recruitment

Participants will contact the research team via email in response to the recruitment advertisements if they are interested in taking part in the study.

6.4 Payment
Participants will be reimbursed for their time at a rate equivalent to £10.55/hour. The total time commitment for each participant is 34 hours. The payment to participants on successful completion of the whole study will be £360. It is essential that participants attend on time for all blood tests across both experiments, therefore, participants will only be paid on successful completion of all aspects of the study. If a participant completes the baseline visit but does not complete experimental visits they will be paid £40. If a participant successfully completes the optional stool sampling assessments they will receive an additional £20. The total potential reimbursement is therefore £380.

6.5 Pre-screening
Prior to the pre-screen, the participant will be emailed a Participant Information Sheet (PIS). This will be done at least 24 hours before the experimental visit. Potential participants will be allowed as much time as need to decide to whether or not to participate. They will then be contacted by one of the researchers by telephone and asked to answer questions relating to their eligibility for the study. They will have the opportunity to ask the researcher questions about the study during the call. If the participants' responses are satisfactory, the participant will be invited for a screening visit.

6.6 Screening
The screening visit will be held at the King's CRF. It will be performed no longer than 28 days prior to IMP administration.

- Gaining informed consent
- Recording demographic details: sex, date-of-birth, ethnicity, previous medical history, medication history, and alcohol and substance use history
- Recording vital signs, height, weight, BMI and body fat content
- Urine drug screen for illicit drug use and pregnancy
- Urinalysis, alcohol breath test
- Blood tests: full blood count (FBC), urea and electrolytes (U&Es) and liver function tests (LFTs)
- Stool sample provided to take home (optional)

6.7 Consent
Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the trial without giving reasons. They will be provided with a contact point where they may obtain further information about the trial. Potential participants should be able to give consent and a person is assumed to have mental capacity to make a decision unless it is shown to be absent. Consent will be taken by medical doctors who are duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Written material consisting of participant information leaflet and consent documentation will be approved by the Research Ethics Committee and will be in compliance with GCP, local regulatory and legal requirements. There will be opportunity for the participant to ask questions to a member of the research team. The patient will be given as much time as required to consider the information and consider their participation. A copy of the consent form and PIS will be given to the participant, with

the original consent filed in the investigator site file and a copy of the consent form in the Case Report Form.

6.8 Randomisation

Subjects will be randomised into the study provided they have satisfied all subject selection criteria. A web based randomisation system will be designed, using the bespoke King's Clinical Trials Unit (KCTU) randomisation system and will ensure each treatment is equally distributed across each study period. The randomisation system will be created in collaboration with the study team and maintained by the KCTU for the duration of the project. It will be hosted on a dedicated server within KCL. The Chief Investigator (CI) or delegate will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate in the first instance.

Participant initials and date of birth will be entered on the randomisation system, NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the study. Randomisation will be undertaken by authorised staff onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

The CI team will undertake appropriate reviews of the entered data, for the purpose of data cleaning. No data can be amended in the system, however CI or delegate may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.
Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

6.9 Blinding and Emergency Unblinding

The study will be double-blind with unblinding occurring at the end of data collection on approval by the Principal Investigator. The capsules will be identical in appearance so both the investigators and participants will remain blinded to treatment allocation. The Maudsley pharmacy will hold treatment allocation information for each participant, with 24-hour non-resident on-call access and can be called at any time to unblind a specific session.

Participants will be monitored before and after dosing and not discharged until medically cleared. Delayed adverse effects to study medications after discharge are unlikely, however, if required emergency unblinding will be provided by the on-call pharmacist. Unblinding protocol and reporting will be applied according to the local pharmacy procedures.

Out of Hours Emergency Contact

Participants will be provided with a contact card when receiving the study medication, so that they can contact the investigators in case of emergency out of hours. The investigator will contact the on-call pharmacist if unblinding is required. Participants will also be instructed to dial 999 or 111 in case of emergency.

6.10 Withdrawal criteria

i. Withdrawal of consent
ii. Significant abnormalities detected during the medical assessment or blood tests at the screening visit
iii. Use of alcohol, illicit substances 24hour before or during experiments
iv. Use of over-the counter medications, health supplements or CBD products
v. Use of prescribed medications (excluding the intrauterine device or intrauterine system)
vi. Suspected Unexpected Serious Adverse Reaction
vii. Participant does not attend follow-up point
viii. Investigator discretion

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw participants from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Withdrawn participants will be replaced.

6. 11 Expected duration of the trial

The end of trial will be defined as the database lock.

7. TRIAL PROCEDURES

7.1 Setting

NIHR-Wellcome Trust Kings Clinical Research Facility (CRF)

7.2 Eligibility Review

The study team will review participants eligibility for the study at the start of each experimental visit. This will include a urine drug screen and alcohol breath test.

7.3 Fasting Requirements

Participants will fast from 10pm the previous evening and will not eat until 4 hours after drug administration on the first day of each experimental visit. Participants will be allowed to drink water only.

7.4 Administration

Drug administration will be at approximately 9am on the first day of each experiment.
Oral administration.
Participants will not be informed which formulation of drug they are being administered.

7.5 Trial assessments

7.5.1 Blood sampling

Blood samples will be drawn at the following time-points on experimental visits:
Pre-dose (0-5mins), 0.5, 1, 2, 3, 4, 5, 6, 8, 24, and 48hrs post-dose. The 24hr and 48hour samples should be taken within 15minutes of the target time.

7.5.2 Vital signs

Vital signs (HR, RR, BP, Temp) will be recorded on experimental visits at the following times: pre-dose and 1, 2 4, 8, 24 and 48hrs post-dose. Urinalysis will be completed 4hrs post-dose. The 24hr and 48hour readings should be taken within 15minutes of the target time.

7.5.3 Adverse events

Participants will be asked to report adverse events at each blood sampling timepoint i.e. pre-dose (0-5mins), 0.5, 1, 2, 3, 4, 5, 6, 8, 24, 48hrs post-dose and at the 7-14 day follow-up visit . Participants will be asked specifically about adverse events including, but not limited to, anxiety, irritability, somnolence, dizziness, disorientation, nausea, abdominal pain, abdominal distension, diarrhoea, vomiting, and flatulence.

7.5.4 Drug Effects Questionnaire (DEQ-5)

The DEQ-5 is questionnaire with five items, for example ‘‘Do you feel a drug effect, right now?’ with the response anchors ‘Not at all’ and ‘Extremely’ (Morean et al. 2013 [9]). It will be recorded on experimental visits at the following times: pre dose and at 1, 2, 4, 8, 24 and 48hrs post-dose.

7.5.5 Gastrointestinal Symptom Rating Scale (GSRS)

The GSRS is a 15-item rating scale which assesses five symptom clusters: reflux, abdominal pain, indigestion, diarrhoea and constipation. Each item is assessed with a 7-point Likert scale. The standard recall period for the scale is 7 days; this will be amended so that it assesses past 24 hours only. The scale will be used pre-dose and at 24 and 48 hours post dose. (28)

7.5.6 Stool Sample / Gut Microbiome (Exploratory analysis)

To assess the effect of the gut microbiome on the CBD’s pharmacokinetics and circulating endocannabinoid levels, a stool sample will be collected prior to each drug administration. Participants will be provided with stool sampling kits at the screening visit. This part of the study is optional.

7.6 Laboratory Procedures

At the screening visit, a blood sample will be taken to test for haematology (FBC) renal function (urea and electrolytes) and hepatic function (liver function tests, including bile acids). These tests will be repeated on experimental visits pre-dose and 4-hours post-dose on experimental visits. The test will be completed by ViaPath and be processed according to standard local procedures.

Urine samples for urinalysis, drug and pregnancy testing will be collected in standard collection pots. The samples will be disposed of as soon as tests are successfully completed.

At the screening visit, participants will be provided with pre-packaged and pre-addressed kits for at-home stool collection. Participants will be asked to mail stool kits before day 1 of each experimental

visits. Kits will be mailed to the Oxford Centre for Microbiome Studies for analysis on the gut microbiome.

On day 1 of each experimental visit, participants will have a venous cannula inserted for collection of blood samples. On days 2 and 3 of each experiment, for the 24 hour and 48 hour time-points, venepuncture will be performed a single sample will be taken. Blood samples will be collected in 5ml EDTA tubes.

Within 10min of collection, the samples will be centrifuged (3000rpm for 10minutes). The plasma will be decanted from the tube into two screw-cap collection tubes and immediately placed in a -20ºC freezer in the CRF. The stored samples will be anonymised with participant ID, visit number and time point. Only the research team will be able to link ID number to participant details. At the end of each day, the samples will be moved to a -80ºC freezer for longer term storage in the King's Clinical Trials Facility.

Only plasma will be stored so that analyses can be completed. No human tissue will be stored at the end of the research. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with the 2004 Human Tissue Act.

7.7 Visit by visit events

7.7.1 Recruitment

Participants will contact the research team via email in response to the recruitment advertisements if they are interested in taking part in the study.

7.7.2 Screening visit

The following interventions and assessments will be completed in order at the screening visits:

i. Informed consent
ii. Collection of demographic information
iii. Medical review and examination
iv. Height, weight, body fat
v. Review of eligibility
vi. Urine sample for urinalysis, pregnancy and illicit drugs testing
vii. Alcohol breath test
viii. Blood sampling
ix. Vital Signs
x. Stool sampling kit provided to take home (optional)
xi. Fasting instructions
xii. Alert card and safety instructions

7.7.3 Experimental Visit

7.7.3.1 Day 1

The following interventions and assessments will be completed in order:

i. Fasting (previous night from 10pm)
ii. Eligibility review
iii. Urine sample for pregnancy and illicit drugs testing

iv. Alcohol breath test
v. GSRS
vi. Intravenous cannulation
vii. Pre dose; 0-5mins: blood sampling; vital signs; DEQ-5
viii. 0 mins: drug administration
ix. 30mins: blood sampling
x. 1 hour: blood sampling; vital signs; DEQ-5
xi. 2 hours: blood sampling; vital signs; DEQ-5
xii. 3 hours: blood sampling
xiii. 4 hours: blood sampling; vital signs; DEQ-5; urinalysis
xiv. 5 hours: blood sampling
xv. 6 hours: blood sampling
xvi. 8 hours: blood sampling; vital signs; DEQ-5; adverse events assessment

7.7.3.1 Day 2

i. 24 hours post dose: blood sampling; vital signs; DEQ-5; GSRS; adverse events assessment

7.7.3.1 Day 3

i. 48 hours post dose: blood sampling; vital signs; DEQ-5; GSRS; adverse events assessment.
ii. Payment via bank transfer (if final visit)
iii. Book follow-up visit (if final visit) and provide a urine pregnancy test (if female)

7.7.4 Washout

There will be a minimum 2 week washout between experimental visits.

7.7.5 Follow-up visit

The follow-up visit will be completed via remote video call 7-14 days after day 1 of experiment 2. Participants will be asked to report adverse events. Female participants of childbearing potential will be asked to confirm the result of a urine pregnancy test completed on that day.

7.8 Planned analyses

Blood samples will be analysed for CBD and its metabolites (including 6-OH-CBD, 7-OH-CBD, 7-COOH-CBD) CBDA, THC, endocannabinoids (including anandamide and 2-arachidonoylglycerol). Additional unplanned analyses of relevant metabolites, biomarkers or inflammatory markers may also be completed. The laboratory analyses will be completed at the University of Turku, Finland. Analyses will be completed once all samples have been collected, at the end of the study. All analyses will be completed in accordance with relevant guidance and legislation.

8. COVID-19

The study's COVID risk assessment highlighted no trial procedures which present risks beyond those which are encountered in routine clinical care (i.e. there are no vulnerable participants and no aerosol generating procedures). Therefore, standard King's College Hospital's guidance on the management of SARS-CoV-2 associated risks will be followed throughout the study. Vaccinations and vaccination status are not relevant to the trial or any of its procedures. If the CRF were to close due to any reason, follow-up and safety assessments will be completed at an appropriate NHS or KCL facility or online.

9. SAFETY

9.1 Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- **Adverse Event (AE)**: Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

- **Adverse Reaction (AR):** Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

- **Unexpected Adverse Reaction (UAR)**: An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the investigator's brochure for CBD.

- **Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that**:**
    - results in death;
    - is life-threatening;
    - required hospitalisation or prolongation of existing hospitalisation;
    - results in persistent or significant disability or incapacity;
    - consists of a congenital anomaly or birth defect.

- **Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

9.2 Investigator Assessment

The investigator will seek information on adverse events from participants at 8 hours, 24 hours and 48 hours after each drug administration. Participants will also be able to spontaneously report adverse events throughout the lifetime of the trial. The investigator will use specific questioning and, as appropriate, examination. Information elicited will be recorded participant's Case Report Form. All

clearly related signs, symptoms, and abnormal diagnostic procedures will be recorded. The clinical course of each event should be followed until resolution or stabilisation.

9.3 Reporting Responsibilities

The sponsors have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy. The KHP-CTO will report SUSARs to the MHRA.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days;
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the sponsor), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

King's College London will undertake all sponsor duties and pharmacovigilance. The Investigator is responsible for ensuring that all adverse events occurring during the study treatment period are recorded on Case Report Forms.

9.4 Premature Termination of the Trial

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the trial's research team, regulatory authority or ethics committee concerned. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial. There are no pre-specified treatment stopping rules.

9.5 Dose adjustment

If the study drug is associated with adverse effects that are a cause for concern, the study can be paused and the dose reduced before further experiments are completed. The study's Principal Investigator will be responsible for this decision and will take into account the incidence of adverse effects, their severity and other relevant factors. If necessary, the sample size of the study may be increased to ensure that the planned number of subjects receive both formulations at the same dose.

10. STATISTICS AND DATA ANALYSIS

10.1 Power analysis

As the means are unknown, we base the power calculation on minimum detectable difference assuming the AUC coefficient of variation in CBD is 50% (Taylor et al. 2018(8)). Since there is no carry-over effect in the study, an appropriate analysis of continuous data from a two-period, two-intervention cross-over trial is a paired t-test (29). For the primary outcome, the bioavailability of lipid versus standard formulation in the fasted state, a paired t-test with n=12 has 80% power, at alpha=0.05 (2 tailed) to detect a 44.5% difference in means.

Previous studies demonstrated increased bioavailability with lipid formulations of 7x(19). The study is adequately powered to demonstrate these differences. This sample size and design satisfies EMA recommendations for design and minimum sample size (n=12) in pharmacokinetic studies for comparing formulations.

10.2 Planned recruitment

The study requires 12 complete datasets. With an expected drop-out rate of 15%, we expect to recruit 14 participants.

10.3 Statistical analysis plan

Pharmacokinetics parameters

Pharmacokinetic parameters will be summarized descriptively. Continuous outcomes will be reported as means with standard deviation. Categorical outcomes will be reported as frequencies. Individual participant's pharmacokinetic data may also be presented in tables and graphs. The plasma concentration-time data will be subject to non-compartmental pharmacokinetic analysis using appropriate computer software applications. Linear and/or log-linear plots will be presented. To assess bioavailability between the formulations, log transformed AUC, C_{max} observations will be entered into a linear mixed model to account for the repeated measures and between subject conditions. Linear contrasts representing the difference between conditions will be expressed as ratio of geometric means along with 95% CI and inference based on $p < 0.05$. Planned analysis will be per protocol.

Protocol violations

All protocol violations, including inclusion/exclusion criteria violations and violations during the trial, will be listed, even if they are believed not to influence any of the results.

Demographics

For all participants, descriptive statistics of demographic (e.g., sex, age, BMI, and other baseline characteristics) will be presented by overall.

Safety measures

Summary tables showing vital signs e.g., body temperature, respiratory rate, pulse rate, and SBP and DBP will be provided at each study time point and changes from baseline.
Individual physical examination will be listed and summarised at each study time point.
Important Medical Event, drug, pregnancy test results during the study will be listed.

Visual Analogue Scales & Drug Effects Questionnaire (DEQ-5)

A summary table of DEQ-5 will be summarised descriptively.

Laboratory results
Laboratory parameters including haematology, blood chemistry, and urinalysis will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

Adverse events
A listing of all individual AEs, AR, UAR, SAE, SAR, and SUSAR will be provided. Summary tables of TEAEs will be presented by system organ class based on the MedDRA terminology list (preferred terms): 1 containing the number of TEAEs (frequency of occurrence, number of participants/patients experiencing the event) by treatment and 1 containing the number of drug related TEAEs (frequency of occurrence, number of participants/patients experiencing the event) per treatment. Additional tables of total counts by treatment and relationship and by treatment and severity will be given.

The final statistical analysis plan will be in place prior to study database lock.

11. TRIAL STEERING, DATA MONITORING AND ETHICS MONITORING COMMITTEES

This is a small pharmacokinetic study with a short duration and short follow-up. Safety and pharmacovigilance are important components of the study but costs of running these committees have to offset against the benefit in such a small trial, and also the minimal expected risk from previous published data where cannabidiol has been used in healthy participants and patients. Therefore, there will be no data monitoring or trial steering committees for this study.

12. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

The Investigators will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsors, Regulators and REC direct access to source data and other documents (e.g. participants' case sheets, blood test reports).

13. ETHICS AND REGULATORY APPROVALS

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to Health Research Authority (HRA), Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor) and the REC within the timelines defined in the Regulations. The KHP-CTO or delegate will upload the final report to EudraCT on behalf of the Sponsor.

14. QUALITY ASSURANCE

This is a small pharmacokinetic study with a short duration and short follow-up where the majority of outcome data will not be available until after laboratory analysis. The benefits of data audit are therefore limited. Data will be made available for inspection and monitoring by relevant authorities on request. Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

15. DATA HANDLING AND MANAGEMENT

The study will adhere to KCL's policy on data management, security and sharing. Participants will provide mobile phone numbers so that we can contact them during the study. If a participant requests, they will be contacted with the study outcome.

The Chief Investigator will act as custodian for the study data and all participant data will be pseudo-anonymised. Data will be collected using source data questionnaires (pen and paper). Each study participant will be given a study ID. Source documents will be named with this ID. The source documents will be kept in locked cabinets. Study data will be transcribed to the Elsevier MACRO EDC system.

All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving Standard Operating Procedure (SOP).

Research data will be stored for a minimum of 10 years following the completion of the study. Case report forms will be scanned so that they can be stored electronically along with other data from the study. We plan to store the data on King's College London Research Data Management system.

Access to the final trial dataset

The trial steering group will have access to the final dataset of the trial. The dataset will also be made available to the study investigators, and the trial statistician.

16. DISSEMINIATION POLICY

Data arising from the trial will be owned by King's College London. It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Where appropriate, the results will be disseminated to the general public by means of press releases, posts on social media and at public engagement events. The Consort Guidelines and checklist will be reviewed prior to generating any publications for the trial. Individual participants will not be identifiable in publications.

17. INDEMNITY

Insurance and indemnity will be provided by King's College London policies.

18. FINANCIAL ASPECTS

Philip McGuire NIHR Senior Investigator Award, Activity Code: RE13018

The study drug and formulation will be provided by SEEK pharmaceuticals.

29. ARCHIVING

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Sponsor Archiving SOP.

20. AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	10/01/2022	Edward Chesney	MHRA recommended changes
1	1.2	07/03/2022	Edward Chesney	Non-substantial

21. SIGNATURES

_____ _____

Chief Investigator
Prof Philip McGuire

Date

12/04/2022

_____ _____

Trial Co-ordinator
Dr Edward Chesney

Date

_____	_____
Trial Statistician	Date
Oranuch Nampaisan	

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