Title

CANNABIDIOL ORO-BUCCAL SPRAY ADMINISTRATION CLINICAL TRIAL

Short Title

CANNABIDIOL ORO-BUCCAL ADMINISTRATION STUDY

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Contents

PROTOCOL SYNOPSIS

Title	**CANNABIDIOL ORO-BUCCAL SPRAY ADMINISTRATION CLINICAL TRIAL**
Objectives	**Primary:** Determine Cannabidiol orobuccal spray administration techniques required to achieve effective orobuccal absorption as evidenced by: (i) Plasma cannabidiol (CBD) levels > 0.5 ng/ml and 1 ng/ml at the 50 min timepoint after a single 2.5 mg and 5 mg CBD dose, respectively. (ii) CBD plasma levels > 10-fold the 7-hydroxy cannabidiol (7-OH-CBD) plasma levels. **Secondary:** (i) Determine the time taken until > 90% of CBD from one spray (2.5 mg CBD) of MC-1020 orobuccal spray is absorbed into the orobuccal mucosa by drinking water to wash oral cavity CBD away at various timepoints and measuring the resultant reduction in serum CBD levels. (ii) Determine if CBD, 7-COOH-CBD and 7-OH-CBD can be detected in saliva.
Study Design	Single dose open label pharmacokinetic study
Intervention	MC-1020 is a Hemp Oil Extract (16.67 mg/mL Cannabidiol) formulated in nano-micelles for oro-buccal administration. One actuation of the pump delivering 150 µL, which contains 2.5 mg CBD.
Planned Sample Size and Site	Total sample size of 10 healthy participants conducted at Medlab Clinical Ltd Alexandria NSW Australia.
Ethical considerations	HREC approval and informed consent
Inclusion Criteria	i. Male or female outpatients 18-85 years of age. ii. Physically and mentally healthy and not currently taking any medications, vitamins, minerals, supplements. iii. The ability to comprehend and satisfactorily comply with protocol requirements. iv. Written informed consent given prior to entering the baseline period of the study.
Exclusion Criteria	i. Any past history of schizophrenia, psychosis, bipolar disorder or major depression. Or any immediate family history of psychosis. ii. Acute suicidality iii. History or substantial risk of heart disease (arrhythmia, ischaemic heart disease, heart failure). iv. Pregnant women, lactating women, and women of childbearing potential who are not using medically accepted forms of contraception (e.g., IUD,

	oral contraceptives, barrier devices, condoms and foam, or implanted progesterone rods stabilized for at least 3 months), or women who are planning on becoming pregnant. Estrogen-based oral contraceptives are not considered reliable forms of contraception during this study due to drug interaction with CBD. v. Participants who have a history of contraindications or adverse reactions to cannabis. vi. Unable to comply with study procedures or assessments. vii. The current use of any dietary and herbal supplements (15 days wash-out period required); viii. The current use of any over-the-counter or prescription medications.
Statistical Procedures Sample Size Calculation: Analysis Plan:	All data will be summarised descriptively using n, mean, median, standard error of mean and 95% confidence intervals for continuous data, and frequency and percent for categorical data. All tests will be conducted two-sided and *p* values of less than 0.05 will be considered statistically significant. All available data used will be treated as for intention–to–treat analyses. All analyses will be conducted with software from STATA for Mac version 15.1 [College Station, Texas].
Duration of the study	4 days. A follow-up telephone call from the study staff will take place on 4 days after completion for each participant.

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
PI	Principal Investigator
SD	Standard deviation
CBD	Cannabidiol
7-COOH-CBD	7-carboxy-cannabidiol
7-OH-CBD	7-hydroxy cannabidiol
PI	Principal Investigator
IP	Investigational Product
ADR	Adverse Drug Reaction
CRF	Case report Form
PISCF	Participant Information Sheet and Consent Form

1. STUDY MANAGEMENT

1.1 Principal Investigators

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1.4 Sponsor

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1.5 Funding and resources

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2. INTRODUCTION AND BACKGROUND

2.1 Background Information

Cannabidiol (CBD) is a prospective new medicine for several indications and low dose CBD has a good safety and tolerability profile that is appropriate for a Schedule 3 (Pharmacist Only) medicine[1-4]. CBD is the major non-psychomimetic active constituent of cannabis and has been shown in randomised controlled clinical trials to have efficacy for treating epilepsy, stress, anxiety, insomnia, psychosis and addiction[5-15]; and CBD has preclinical evidence for efficacy as an antidepressant, antiemetic, analgesic and anti-inflammatory[2,13,14,16]. Currently CBD products (edibles, tinctures and vape) are widely used around the world with more than 10% of adult populations having tried them for medicinal purposes[17,18]. Low dose CBD is commonly used to treat self-perceived anxiety and depression, stress, insomnia, pain, and skin conditions[18,19]. Most purchases are from online suppliers and are not of good pharmaceutical standards[18]; and there is a need for good pharmaceutical quality low dose CBD product to be available with evidence-based claims.

Low dose CBD has a good safety and tolerability profile, with few adverse effects[4]. Unlike THC, CBD is not psychomimetic and does not cause intoxication, euphoria, addiction, psychomotor impairment, or cognitive impairment[20-22]. Importantly, low dose CBD (less than 150 mg/day) does not cause the hepatocellular injury observed for higher dose CBD (>600 mg /day)[23-26]. Reviews of 49 clinical trials of CBD, including intravenous, inhalation and oral routes of administration and oral dose ranges of 10 – 1500 mg per day, found that CBD was well tolerated with a good safety profile[2,4]. CBD has also been shown to have no potential for abuse or dependence in humans[27-30]. High-dose CBD has drug-drug interactions with medicines metabolised by the Cytochrome P450 pathways[31] and it is not yet known the extent that this occurs with low dose CBD. There is the possibility of mild drowsiness and fatigue with low dose CBD[31].

CBD is a small lipophilic molecule that has erratic gastrointestinal absorption and is subject to first pass metabolism. Ingestion of CBD leads to highly variable systemic concentrations and a slow and erratic an onset of action[32]. Up to 75% of THC in ingested cannabis-based medicines is subject to first pass metabolism[3,33], and first pass metabolism of CBD appears similar[34,35]. Inhaled cannabis-based medicines bypass first-pass metabolism and result in ten-fold higher plasma levels of THC and CBD than the plasma levels of their major metabolites, 11-OH-THC and 7-OH-CBD, respectively[34]. After oral administration, 7-OH-CBD is further metabolized to 7-COOH-CBD, the plasma levels of which are 10-fold that of 7-OH-CBD and CBD[36]. In contrast, plasma levels of 11-OH-THC and 7-OH-CBD from ingested cannabis-based medicines are usually of similar levels to that of THC and CBD, respectively[34]. However, inhaled CBD is likely to require frequent dosing for a maintenance therapy [32,37] and may lead to long-term damage from toxic chemicals caused by oxidization of CBD and excipients at the high temperatures involved with both smoking and vaping [31,32]. Oral mucosal absorption of CBD could provide suitable delivery of CBD that avoids first pass metabolism. However, sublingual drops and an ethanol-vehicle buccal spray have so far been reported to provide similar relative metabolite levels to ingested cannabis-based medicines[34,35], which indicates that the majority of the medicine is swallowed and not absorbed across the oral mucous membrane.

Preliminary data (Vitetta L., et al.) for the administration of micellized THC and/or CBD buccal spray shows mixed results with some administrations resulting in time to peak serum cannabinoid levels

(T_{max}) < 45 min and a low level of metabolites; however, some administrations show $T_{max} \geq 1$ hr and a high level of metabolites. This suggests that sometimes the micellized cannabinoids in the oro-buccal spray are being absorbed across the oro-buccal mucosa; however, sometimes they are not and are being swallowed. The aim of this study is to determine if it is possible to administer the MC-1020 oro-buccal spray so as to reliably achieve mucosal absorption of CBD and to understand some of the factors affecting mucosal absorption of CBD administered by the MC-1020 oro-buccal spray.

2.2 Research Question

This study will explore if it is possible to administer MC-1020 oro-buccal spray so as to reliably achieve mucosal absorption of CBD and to understand some of the factors affecting mucosal absorption of CBD administered by the MC-1020 oro-buccal spray .

2.3 Rationale for Current Study

Ingested CBD has poor and erratic bioavailability and is subject to up to 75% first pass metabolsm, which could be improved by oro-buccal delivery. However, attempts at oro-buccal delivery to-date have failed as evident from the high levels of first pass metablolites present in the plasma[34,35]. Preliminary data from micellized cannabinoid oro-buccal sprays indicate that the NanoCelle™ technology used to create these cannabinoid micelles, may be able to facilitate oro-buccal mucosa absorption; however, successful administration has been inconsistent. If reliable buccal mucosa absorption can be demonstrated and the critical factors for achieving this understood, a delivery mechanism for cannabinoids that is suitable for routine medical use could be provided.

3 STUDY OBJECTIVES

3.1 Primary Objective

Determine Cannabidiol orobuccal spray administration techniques required to achieve effective orobuccal absorption as evidenced by:

(i) Plasma cannabidiol (CBD) levels > 0.5 ng/ml and 1 ng/ml at the 50 min timepoint after a single 2.5 mg and 5 mg CBD dose, respectively.

(ii) CBD plasma levels > 10-fold the 7-hydroxy cannabidiol (7-OH-CBD) plasma levels.

3.2 Secondary Objectives

(i) Determine the time taken until > 90% of CBD from one spray (2.5 mg CBD) of MC-1020 orobuccal spray is absorbed into the orobuccal mucosa by drinking water to wash oral cavity CBD away at various timepoints and measuring the resultant reduction in serum CBD levels.

(ii) Determine if CBD, 7-COOH-CBD and 7-OH-CBD can be detected in saliva.

4. STUDY DESIGN

4.1 Type of Study

Single dose open label pharmacokinetic study

4.2 Study Design

This study (shematic on page 14) involves administering a single dose of a CBD buccal spray on each of four days and measuring plasma CBD and its major metobilte 50 minutes after each dose. There will be ten participants and half will administer 2.5 mg doses and the other half will administer 5 mg doses of CBD throughout.

SCREENING (Day -14 to Day -1):

Prospective healthy participants, 18-85 years of age will be recruted and the following performed:

1. Participant Information Sheet provided and Informed Consent
2. Baseline pathology test: Urine pregnancy test (if applicable).

Ten participants who satisfy the inclusion and exclusion criteria will be invited to participate in the study.

Participants will be monitored for adverse events from the time the informed consent is signed (Day -14 to Day -1) until follow-up (Day 8).

TREATMENT (Day 1 to Day 4):

On the morning of each dosing day, participants will be admitted into the facility. Vital signs will be measured and on the first day only, women of childbearing potential will undergo a urine pregnancy test. Participants will also be randomised on the first dosing day. Participants A1, B1, C1, D1 and E1 will always administer one spray (2.5 mg CBD). Participants A2, B2, C2, D2 and E2 will always administer two sprays (5 mg CBD), which will be done by administering one spray to each cheek.

Participants will fast from 1 hr before to 1 hr after their CBD dose on each day. Teeth will be cleaned with a fresh toothbrush without toothpaste 15 min before administration. Particpants will avoid swallowing for 5 minutes after each dose and avoid spraying on their tongue. Spray will be directed to either, the inside of their cheek/s or the lower pouch between gum and cheek.

Blood (5 ml) and sputum (2.5 ml; no pharmacological inducement) will be collected at 50 min. Blood will be collected in EDTA tubes for plasma isolation and CBD, 7-COOH-CBD and 7-OH-CBD assays. Saliva will collected in sterile specimen jars. Blood and saliva will be spun down at 2000xg for 15 min at 6 ^{o}C and plasma and saliva supernatant stored in 500 ul aliquots at -20 ^{o}C (total number of blood samples = 40; saliva samples = 22). CBD, 7-COOH-CBD and 7-OH-CBD assays will be performed independently by Agilex Biolabs Pty Ltd, 28 Dalgleish Street, Thebarton, SA 5031 Australia.

Day 1: Spray to cheek; Blood and saliva collected.

Day 2: Spray to lower oral pouch; Blood only collected.

Day 3: Spray to cheek except that participant will swallow all saliva immediately after the dose; Blood and saliva collected.

Day 4: Spray to cheek except that a glass of water will be drunk after dose as follows:

Participant A1 & A2: 30 sec; Blood and saliva collected.

Participant B1 & B2: 1 min; Blood only collected.

Participant C1 & C2: 2 min; Blood only collected.

Participant D1 & D2: 4 min; Blood only collected.

Participant E1 & E2: 8 min; Blood only collected

Participants will remain on site for 4 hours after each dose and vital signs and symptoms checked before release home. If any abnormality is found or reported the participant will be referred for immediate medical examination at a local general practice or accident and emergency.

FOLLOW-UP (Day 8):

On day 8, Participants will be contacted by phone by the study team and any adverse reactions recorded. If any abnormality is reported the participant will be referred for immediate medical examination at a local general practice or accident and emergency.

4.3 Number of Participants

A total sample size of n = 10 healthy participants at one site.

4.4 Study site

Medlab Clinical Ltd, 66 McCauley St, Alexandria NSW 2015.

4.5 Expected Duration of Study

- Expected start June 2022 and stop date July 2022.
- Expected time period for the recruitment phase of the study is 1 month

4.6 Primary and Secondary Outcome Measures

Primary Objective

Determine MC-1020 orobuccal spray administration techniques required to achieve effective orobuccal absorption as evidenced by:

(i) Plasma cannabidiol (CBD) levels > 0.5 ng/ml and 1 ng/ml at the 50 min timepoint after a single 2.5 mg and 5 mg CBD dose, respectively.

(ii) CBD plasma levels > 10-fold the 7-hydroxy cannabidiol (7-OH-CBD) plasma levels.

Secondary Objective

(i) Determine the time taken until > 90% of CBD from one spray (2.5 mg CBD) of MC-1020 orobuccal spray is absorbed into the orobuccal mucosa by drinking water to wash oral cavity CBD away at various timepoints and measuring the resultant reduction in serum CBD levels.

(ii) Determine if CBD, 7-COOH-CBD and 7-OH-CBD can be detected in saliva.

5. STUDY TREATMENT

5.1 MC-1020 (Medlab Clinical)

MC-1020is a Hemp Oil Extract (16.67 mg/mL Cannabidiol) formulated in nano-micelles for administration by pump action of a fine mist spray to the oro-buccal mucous membrane (Refer to *Investigator Brochure* for details). One actuation of the pump delivering 150 μL, which contains 2.5 mg CBD. For multiple sprays, alternate cheeks will be used with a 2 minutes wait before applying to the same cheek. Participants will be instructed on how to administer MC-1020, including alternating cheeks for more than one spray per dose, dosing while at rest (sitting) and without talking.

Active ingredient: Cannabidiol (CBD) from Hemp oil extract.
Each 1mL MC-1020 oro-buccal spray contains 16.67 mg cannabidiol (CBD).
Each 150 microlitre spray contains 2.5 mg CBD.
Each 150 microlitre spray also contains up to 0.165 mg potassium sorbate.
MC-1020 contains modified vegetable oil, glycerol, peppermint oil, medium-chain triglyceride, potassium sorbate, and sucralose as inactive ingredients.
MC-1020 is supplied as

- Bottle size: 30 mL;
- Bottle material: amber glass Type I;
- Filling Quantity: 30.5mL (30 mL as per label claim, plus 0.5 mL overage);
- Spray: 150 μL / spray (total 200 sprays/bottle as per label claim, plus 10 sprays overage);
- Label Claim: 16.67 mg/mL CBD;
- Per spray (i.e., per actuation): 2.5 mg CBD/150 μL;

MC-1020 should be stored at RT [15°–30°C (59°–86°F], protected from direct sunlight within a restricted area of the clinical trial Pharmacy.

5.2 Excluded medications and treatments

Levodopa, Sildenafil (or any other PDE5s are excluded on safety grounds) and any hypersensitivity to cannabinoids.

6. PARTICIPANT ENROLLMENT AND RANDOMISATION

6.1 Recruitment

Participants will be recruited from advertisements placed at local general practice, universities and workplaces.

6.2 Eligibility Criteria

6.2.1 Inclusion Criteria

At Screening Phase
Participants must fulfil all of the following criteria:

i. Male or female outpatients 18-85 years of age.
ii. Physically and mentally healthy and not currently taking any medications, vitamins, minerals, supplements.
iii. Participants must agree to abstain from medicine, supplements, alcohol and recreational cannabis use for the duration of the study.
iv. The ability to comprehend and satisfactorily comply with protocol requirements.
v. Written informed consent given prior to entering the baseline period of the study.

6.2.2 Exclusion Criteria

At Screening Phase
Participants will be excluded if they meet any of the following criteria that include:

i. Any past history of schizophrenia, psychosis, bipolar disorder or major depression. Or any immediate family history of psychosis.
ii. Acute suicidality
iii. History or substantial risk of heart disease (arrhythmia, ischaemic heart disease, heart failure).
iv. Pregnant women, lactating women, and women of childbearing potential who are not using medically accepted forms of contraception (e.g., IUD, oral contraceptives, barrier devices, condoms and foam, or implanted progesterone rods stabilized for at least 3 months), or women who are planning on becoming pregnant. Estrogen-based oral contraceptives are not considered reliable forms of contraception during this study due to drug interaction with CBD.
v. Participants who have a history of contraindications or adverse reactions to cannabis.
vi. Unable to comply with study procedures or assessments.
vii. The current use of any dietary and herbal supplements (15 days wash-out period required);
viii. The current use of any over-the-counter or prescription medications.

Early termination or drop–out from the study relevant to the following criteria:

i. severe adverse or severe specific adverse effects side effects or significant clinically assessed deterioration in physical or mental health;
ii. violation of LHDs treatment centre guidelines and conditions (e.g., violence towards staff or other patients);
iii. non-compliance with trial protocol.

6.3 Informed Consent Process

The entire informed consent process will involve giving a prospective participant:

- Clear and adequate information concerning the clinical intervention study that is about to begin, namely the various stages of the study,
- Providing adequate opportunity for the participant to consider all options,
- Responding to the participant's questions,
- Ensuring that the participant has understood all information,
- Obtaining the participant's voluntary agreement to participate and,
- Continuing to provide information as the subject or situation requires.
- Documentation that clearly states they are participating in a clinical trial and this will be clearly outlined in the appropriate and relevant PISCF for all stages of the clinical study.

A research Co-ordinator / Nurse will be responsible for administering the participant information sheet and consent form.

The following line will be adopted for an effective discourse between participant and investigator:

1. The consent document will be used as a guide to explain the study to a prospective participant.
2. The consent document will constitute the basis for a meaningful verbal exchange between the prospective participant and the research investigator and this document will NOT serve as a substitute for discussion.

3. The process will provide ample opportunity for the Investigator and the subject to exchange information and ask questions.
4. Any questions relevant to the study and its procedures arising from the exchange will be clearly detailed to the participant prior to seeking consent.
5. Once all queries have been answered and study procedures understood by the participant, documentation will be provided to the participant and a written consent form containing all the information to be disclosed and signed by the participant will be obtained and a copy provided to the participant.

6.4 Enrolment and Randomisation Procedures

Participants identified as eligible by meeting all inclusion and exclusion criteria to participate and who have subsequently completed and signed an informed consent will be enrolled into the randomised Phase of the study. The participant will receive a study enrolment number, and this will be documented in the participant's medical record and on all study documents.

6.5 Participant Withdrawal

6.5.1 Reasons for withdrawal

Taking a harm minimization/best interest approach, removing a patient from the clinical study will be at the clinical discretion of PI from the research site, in consultation with other members of the research team and the treating clinician, and if agreed upon the PI may remove any participant from the clinical study at any time if:

1. A participant's safety may be compromised (e.g., serious adverse event(s) or unanticipated health problems);
2. The study is terminated by the investigator or sponsor related to increased risk to participants;
3. The participant is non-compliant with the study protocol / procedures;
4. The PI determines that it is in the best interest of the participant to be removed from the study.

6.5.2 Replacements

There will be no replacements.

6.6 Trial Closure

Pertaining to investigator(s):

1. Provide a summary report of the trial's outcome to the ethics committee as required.
2. Keep documentation and correspondence in the trial master file in accordance with Good Clinical Practice.
3. Inform the sponsor of the completion of the study.
4. Ensure arrangements for archiving of trial documents are clarified.
5. Ensure appropriate final disposition of any investigational product, and this may include return to the sponsor or destruction of remaining materials.

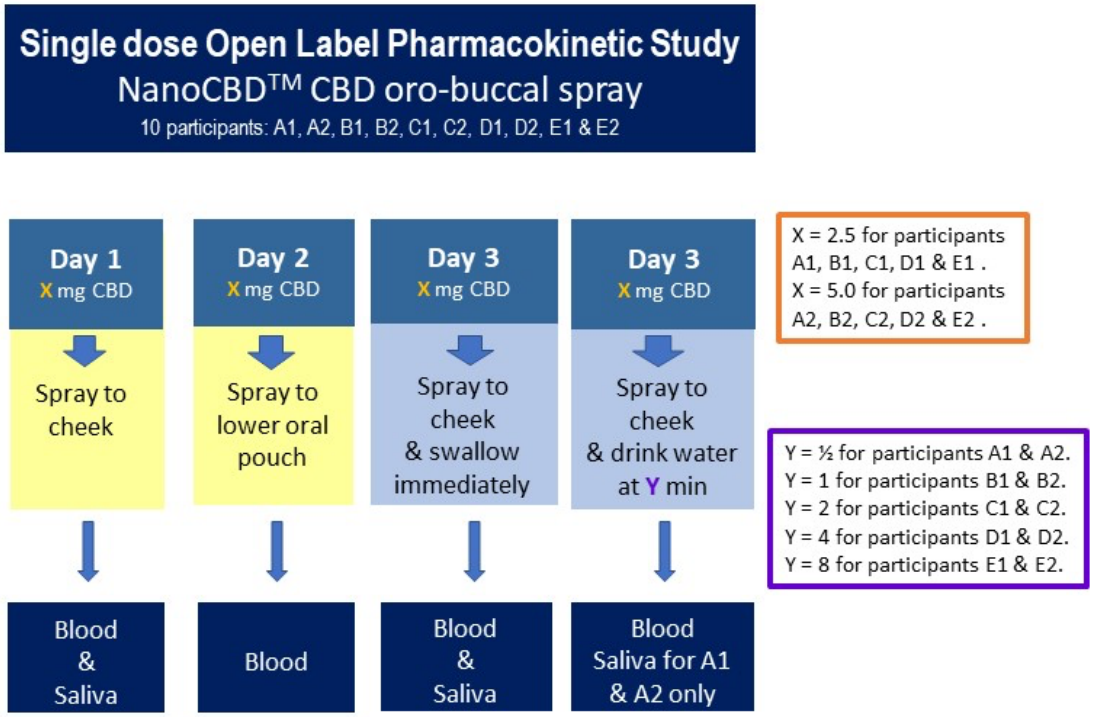
Pertaining to Participants:

Participants will be followed up for the development of adverse events for one month following completion of the clinical study or in the event that participants withdraw from the study

(participants are encouraged to contact the study team should they develop an adverse event up to three months following completion of the clinical study). Follow-up procedures may include telephone calls to the participant and/or outpatient visits as needed. All participants who withdraw from the study with an ongoing adverse event must be followed until the event is resolved or deemed stable by the PI.

7. VISITS AND PROCEDURES SCHEDULE

Study Flow Chart



8. ADVERSE EVENT REPORTING

Adverse event reporting for clinical trials involving therapeutic products, must meet the requirements of the National Health and Medical Research Council, Australian Health Ethics Committee (AHEC) Position Statement "*Monitoring and reporting of safety for clinical trials involving therapeutic products*" (May 2009), which can be found at:

https://www.nhmrc.gov.au/guidelines-publications/e112

8.1 Definitions

An adverse event for medicines is also referred to as an adverse experience, any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable or unintended sign, symptom or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

8.2 Assessment and Documentation of Adverse Events

For this clinical study, an adverse event (AE) is defined as any unfavourable and unintended change in the:

- signs, symptoms or chemistry (abnormal lab result) that the participant experiences temporarily associated with the use of the sponsor's product, whether or not considered related to the use of the product;
- worsening of a pre-existing condition or symptom.

The assessment will be undertaken by a physician investigator with Research Co-ordinator / Nurse assistant to the PI. They will record the information experienced by the participant including:

- all laboratory data / results (e.g. raised Gama GT, hypocalcaemia)
- all adverse experiences such as reported from common cannabis treatment related adverse events, including most mild to moderate severity AEs, psychosis, somnolence, dizziness, confusion, vomiting, hypotension, blurred vision, drowsiness, dry eyes, visual hallucinations, relaxation, coordination disturbance, euphoria, headache, and nausea.

8.3 Eliciting Adverse Event Information

Eliciting adverse event information of drug harm and tolerability rely, in part, on clinical trial participant reports of adverse events (AEs), medical histories and concomitant medications.

Recognize:

- the difference between a non-serious adverse event and a serious adverse event
- a suspected adverse reaction
- unexpected or unanticipated adverse event

Differentiate:

- between severity and serious adverse event

8.4 Serious Adverse Event Reporting

8.4.1 SAEs

Serious adverse event (SAE):

An unforeseen medical event that occurs in the course of clinical research that:

- results in participant death.
- is life-threatening to the participant.
- requires the inpatient hospitalisation or prolongation of existing hospitalisation for the participant or leads to the participant having a persistent or significant disability/incapacity.

For medicines, also referred to as serious adverse drug reaction, any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

NOTE: The term 'life-threatening' in the definition of 'serious', refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

8.4.2 SUSARs

Suspected Unexpected Serious Adverse Reaction (SUSAR)

All adverse events that are suspected to be related to an investigational medicinal product and that are both unexpected and serious are considered to be SUSARs.

A serious adverse event for which there is some degree of probability that the event is an adverse reaction to the administered drug and the adverse reaction is unexpected.

Serious event NOT outlined in the study protocol or information sheet.

8.5 Specific Safety Considerations (e.g., Radiation, Toxicity)

Eligible participants will be monitored for AEs associated with increased risk of developing psychosis or suicidal ideation due to the administration of the treatment medicines.

9. STATISTICAL METHODS

All data will be summarised descriptively using n, mean, median, standard error of mean and 95% confidence intervals for continuous data, and frequency and percent for categorical data. All tests will be conducted two-sided and *p* values of less than 0.05 will be considered statistically significant. All available data used will be treated as for intention–to–treat analyses. All analyses will be conducted with software from STATA for Mac version 15.1 [College Station, Texas].

10. DATA MANAGEMENT

10.1 Data Collection

Clinical trial data acquisition will be according to the CRF and will follow the data flow from the perspective of the investigator completing the CRF. This process will take into account the flow of study procedures and typical organization of data in a medical record.

10.2 Data Storage

Clinical case reports will be manually completed and stored in locked file cabinets at the study site.

CRF data will be transferred to an electronic database and be securely maintained on an electronic disk that is password protected. This dataset will be located and maintained at Write Source Medical with the independent statistician (Dr. Belinda Butcher), at PO Box 1521| Lane Cove NSW 2066, Australia.

10.3 Data Confidentiality

In order to protect participant information privacy, all data will be de-identified and will be recorded with a unique identifier and as such will be re-identifiable. Furthermore, note that the master list containing participant identifiers will remain at the study site.

10.4 Study Record Retention

This study will incur a moderate risk to participants and as such the files will be retained in a suitable repository for a minimum of 15 years and will be funded by the sponsor.

11. ADMINISTRATIVE ASPECTS

Prior to participant enrolment the clinical trial will be registered with the Australia New Zealand Clinical Trials Registry – ANZCTR. Reference number will be provided.

11.1 Independent HREC approval

Prior to participant enrolment the clinical trial will have been approved by appropriate Local Health District HREC.

11.2 Amendments to the protocol

Any amendments will be submitted to the HREC for review prior to implementation as per HREC guidelines.

11.3 Protocol deviations

Any protocol deviations will be submitted to the HREC for review.

11.4 Participant reimbursement

Participants will be reimbursed for parking and meals on trial days at study site.

11.5 Financial disclosure and conflicts of interest

Medlab Clinical Ltd. is the sponsor of the study and the entity involved in developing the cannabis medicine.

Dr Jeremy Henson and Professor Luis Vitetta are employees of Medlab Clinical Ltd.

12. USE OF DATA AND PUBLICATIONS POLICY

This study will most likely be the subject of invited plenary presentations at national and international meetings and will likely result in influential publications. Participant privacy will be maintained as no participant will be individually identified in any publication.

Furthermore, we note that this protocol will adhere to SPIRIT which will enhance the transparency and completeness of the trial protocol for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders [38,39].

13. REFERENCES

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2 Bergamaschi, M. M., Queiroz, R. H., Zuardi, A. W. & Crippa, J. A. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Curr Drug Saf* **6**, 237-249, doi:10.2174/157488611798280924 (2011).

3 Fasinu, P. S., Phillips, S., ElSohly, M. A. & Walker, L. A. Current Status and Prospects for Cannabidiol Preparations as New Therapeutic Agents. *Pharmacotherapy* **36**, 781-796, doi:10.1002/phar.1780 (2016).

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