ABSTRACT

Introduction The non-intoxicating plant-derived cannabinoid, cannabidiol (CBD), has demonstrated therapeutic potential in a number of clinical conditions. Most successful clinical trials have used relatively high (≥300 mg) oral doses of CBD. Relatively few studies have investigated the efficacy of lower (<300 mg) oral doses, typical of those available in over-the-counter CBD products.

Methods We present a protocol for a randomised, double-blind, placebo-controlled, parallel-group clinical trial investigating the effects of a low oral dose (150 mg) of CBD on acute psychosocial stress, situational anxiety, motion sickness and cybersickness. Participants (n=74) will receive 150 mg of CBD or a matched placebo 90 min before completing three virtual reality (VR) challenges (tasks) designed to induce transient stress and motion sickness: (a) a 15 min ‘Public Speaking’ task; (b) a 5 min ‘Walk the Plank’ task (above a sheer drop); and (c) a 5 min ‘Rollercoaster Ride’ task. The primary outcomes will be self-reported stress and nausea measured on 100 mm Visual Analogue Scales. Secondary outcomes will include salivary cortisol concentrations, skin conductance, heart rate and vomiting episodes (if any). Statistical analyses will test the hypothesis that CBD reduces nausea and attenuates subjective, endocrine and physiological responses to stress compared with placebo. This study will indicate whether low-dose oral CBD has positive effects in reducing acute psychosocial stress, situational anxiety, motion sickness and cybersickness.

Ethics and dissemination The University of Sydney Human Research Ethics Committee has granted approval (2023/307, version 1.6, 16 February 2024). Study findings will be disseminated in a peer-reviewed journal and at academic conferences.

Trial registration number Australian New Zealand Clinical Trials Registry (ACTRN12623000872639).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will use a rigorous randomised, double-blind, placebo-controlled design to investigate the effects of a low oral dose (150 mg) of cannabidiol (CBD).
⇒ The dose of CBD provided (ie, 150 mg) will be comparable to those available over-the-counter in many countries.
⇒ Virtual reality will be used to administer safe, realistic and precisely reproducible test paradigms that induce transient stress and nausea in volunteers.
⇒ Blood samples will not be obtained to verify plasma CBD concentrations as venepuncture has the potential to induce extraneous stress.

INTRODUCTION

Cannabidiol (CBD) is a non-intoxicating constituent of the Cannabis sativa plant.1 2 It has a good safety and tolerability profile and a diverse range of pharmacological targets, including the serotonin receptors (eg, 5-HT1A), G protein-coupled receptors (eg, GPR55 and GPR18) and transient receptor potential ion channels (eg, TRPA1).3–10 CBD has demonstrated therapeutic potential in several clinical conditions,4 5 including anti-convulsant effects in paediatric epilepsy,11–13 anxiolytic effects in anxiety disorders,14 15 antipsychotic effects in schizophrenia,16 17 and ‘anti-addiction’ effects in substance use disorders.18 19 These clinical benefits are typically observed at relatively high oral doses of CBD (eg, ~300–1500 mg).4 5

In regions such as North America and Europe, CBD is available as both a prescription drug and a ‘nutraceutical product’.20 These nutraceutical or ‘wellness’ products are typically oral formulations (eg, oils, capsules, gummies) that contain low doses of CBD (ie, ≤150 mg/day) and are widely available in health food stores and pharmacies.20 21 In Australia, regulation of ‘low-dose CBD products’ (containing ≤150 mg/day) was recently eased to allow patients without a prescription
access to registered products in pharmacies. However, registration of such products requires approval by Australia’s medicines regulator based on demonstrated efficacy and safety. With no products having been registered in the ~3 years since these regulatory changes were enacted (December 2020), questions about whether CBD can demonstrate efficacy at these lower doses have been raised.

Indeed, a recent review found little high-quality evidence to support the efficacy of CBD (in any conditions) at doses ≤200mg. This review acknowledged, however, that such doses were under-studied. Some promising results have been obtained with public speaking tasks designed to induce ‘psychosocial stress’ in healthy volunteers when 300 mg CBD was administered. Therefore, further research investigating the anxiolytic effects of low to moderate oral doses of CBD is warranted. It should be noted that the oral bioavailability of CBD is limited (~13%–19%) but may be enhanced by certain lipid-rich formulations or by administration with fatty foods. The current study will use a proprietary blend of tocopherol phosphates (so called ‘Tocopheryl Phosphate Mixture’ (TPM), which has been shown to increase the bioavailability of lipid-soluble substances.

Virtual reality (VR) technologies are increasingly being used to investigate psychosocial stress and anxiety in laboratory studies. This approach allows for minimal resourcing relative to ‘real-world’ studies, customisable and reproducible test paradigms and the accurate monitoring and recording of key outcomes. Furthermore, VR provides the advantage of simulating physiologically provoking activities without real danger, for example, walking a plank over a sheer drop. However, the use of VR is often accompanied by motion sickness (a pattern of symptoms that arise from exposure to stimuli involving significant visual or physical motion) and cybersickness (a subtype of motion sickness that arises specifically due to exposure to VR). CBD has shown antinausea and antiemetic effects in preclinical studies involving laboratory animals. Interestingly, two of these studies demonstrated that CBD administered intraperitoneally at low doses (2.5–10 mg/kg) but not higher doses (25 and 40 mg/kg) reduced toxin-induced vomiting in house musk shrews. CBD also reduced vomiting in human studies when used in combination with Δ⁹-tetrahydrocannabinol to treat chemotherapy-induced nausea and vomiting. Accordingly, the current study will investigate CBD’s possible antinausea effects in participants by exposure to VR scenarios.

We have developed a series of three unique VR challenges for the current trial. The ‘Public Speaking’ task was adapted from studies that explored the anxiolytic effects of CBD during public speaking challenges and will allow us to determine the effects of CBD during social threat (ie, psychosocial stress). The 5 min ‘Walk the Plank’ task has been modified from previous VR studies requiring participants to walk along a narrow virtual plank above a precipitous drop, inducing physiological markers of acute anxiety (ie, ‘situational anxiety’). Finally, the ‘Rollercoaster Ride’ task challenges participants to complete a virtual rollercoaster ride and has been modelled from VR rollercoaster ride paradigms that have been reliably used to induce motion sickness and cybersickness in participants.

In summary, the current protocol describes a study that aims to investigate the effects of low-dose (150 mg) CBD versus placebo on VR-induced acute psychosocial stress, situational anxiety, acute motion sickness and cybersickness in healthy individuals.

**METHODS**

**Study design**

This study is a randomised, double-blind, placebo-controlled, parallel-group, clinical trial comparing the efficacy of low-dose CBD (150 mg) versus placebo. The study is known as the CAPSTAN (Cannabidiol for Acute Psychosocial Stress and Nausea) clinical trial. A crossover design was deemed unsuitable due to the high likelihood of trial-order effects (eg, habituation to the VR scenarios).

The trial sponsor is the University of Sydney, and the trial site is the Brain and Mind Centre in Sydney, Australia. The study has been approved by the University of Sydney Human Research Ethics Committee (HREC; 2023/307, version 1.6, 16 February 2024) and registered on the Australian New Zealand Clinical Trials Registry (15 August 2023). The study is financially supported by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for cannabinoid research at the University of Sydney. Recruitment commenced on 9 October 2023 and is anticipated to conclude in mid-2024.

**Participant population**

**Inclusion criteria**

We aim to recruit 74 participants who will be: (a) healthy adults aged between 18 and 50 years; (b) proficient in English and able to provide informed consent; (c) residing in the Greater Sydney region of New South Wales, Australia and (d) willing to follow the protocol requirements.

**Exclusion criteria**

The following exclusion criteria will apply:

- Self-reported regular use (ie, more than two times a week) in the past 2 weeks of:
  - Cannabinoid-containing products (eg, cannabis or CBD).
  - Psychotropic drugs (prescriptive or illicit) (eg, cannabis, amphetamines, cocaine, ecstasy (MDMA), LSD (acid), antidepressants, antiepileptics, opioids, benzodiazepines).
- Medication that may affect the stress response (eg, corticosteroids, beta-blockers).
- Self-reported history of allergic reaction (eg, urticaria or anaphylaxis) to cannabis or cannabinoid-containing products.
Frequent (ie, more than weekly) use of VR technology (or suspected drug and/or alcohol dependence as determined by the trial physician).

A chronic medical condition (mental or physical) that is uncontrolled, that is, has been either newly diagnosed, or previously diagnosed and remains symptomatic.

Self-reported high vulnerability to cybersickness or motion sickness.

Current depression, anxiety and stress scores outside the ‘healthy range’ on the Depression Anxiety Stress Scale-21 (ie, >moderate scores for depression (>20), anxiety (>14) and stress (>25)).

A history of repeated episodes of syncope.

Self-reported intense fear of heights.

Participants will be recruited via social media, word of mouth, printed or online study advertisements and direct emails to individuals who have previously registered their interest in participating in clinical trials with the Lambert Initiative for Cannabinoid Therapeutics. Participation is voluntary, and participants can withdraw at any time. Participants will be reimbursed with a $200 gift voucher as compensation for time and expenses incurred as a result of study participation.

The investigational product (Avecho Biotechnology Limited, Victoria, Australia) is an oil-based, soft-gel capsule. Each gel capsule contains 75 mg of pure, synthetic (-)-CBD enantiomer and 75 mg of TPM in medium chain triglyceride oil. The capsules do not contain any other cannabinoids or cannabis constituents.

CBD is generally considered to have a good safety profile. In previous studies, 150 mg CBD caused a very low frequency of mild adverse events (AEs) that did not differ from placebo. The current study’s comprehensive screening and exclusion criteria aims to reduce the likelihood of AEs.

A dose of 150 mg of CBD (ie, two soft-gel capsules) will be administered orally.

The control is a matched placebo. The placebo is identical to the intervention but contains no CBD and will also be administered via oral ingestion.

Participants will be randomised to one of two possible treatments in a 1:1 ratio at the beginning of their Test Day. Specifically, they will be assigned a unique randomisation number that is linked to a treatment via a prepopulated randomisation schedule. The schedule will be generated in seven balanced blocks of 10 and one balanced block of four by an independent statistician using an online random number generator and stored in a password-protected system inaccessible to blinded study personnel (centralised computerised randomisation). The schedule will only be available to the statistician, an independent researcher and the company that will package and label the treatments (Central Pharmacy Logistics).

Treatment allocation will be concealed using numbered containers (or ‘sachets’). Each ‘dose’ will be packaged in a separate, opaque, aluminium sachet labelled with a unique randomisation number.

As this is a double-blind study, participants and the remainder of the research team will not be aware of the assigned treatment. In the event of an emergency, the principal investigator (PI) or trial physician may request the unblinding of a participant for medical care.

Eligibility screening

A study flowchart is presented in figure 1. Willing volunteers will complete a comprehensive online Screening Questionnaire using the ‘Research Electronic Data Capture’ (REDCap) web-based system (~20 min). Volunteers are required to complete a compulsory online declaration tick-box at the start of the questionnaire consenting to the use of the information they provide to evaluate their eligibility. The questionnaire will assess their eligibility to participate. Each volunteer who

Recruitment and retention

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attempts the Screening Questionnaire will be assigned a unique screening number to anonymise their identifying information. The trial physician will review volunteers’ responses and decide on their eligibility for the trial. They will document their decision by completing an eligibility declaration form and a prescription for the trial drug (valid only when the volunteer has been randomised).

**Enrolment**

Eligible participants will be invited to complete a tele-health interview with the trial coordinator. Here, they will receive detailed information about the trial procedures and risks and be informed that their enrolment requires a negative urine drug and pregnancy screen at the start of the experimental procedures (ie, the ‘Test Day’). The trial coordinator will invite the volunteer to ask questions and to discuss participation in the trial with the trial doctor, or to take additional time to consider their decision to participate. Once the trial coordinator is confident that the volunteer understands the requirements of the trial, they will request that the participant sign the informed consent form (see online supplemental file 1). The trial coordinator will then counter-sign the consent form, collect basic demographic information and book the participant for a Test Day.

**Experimental procedure**

Each participant will complete one Test Day (~3 hours) at the Brain and Mind Centre at the University of Sydney (table 1).

**Standardisation procedures**

Prior to each onsite Test Day, participants will be instructed to: (a) abstain from alcohol (≥24 hours); (b) avoid greater than one standard serving of caffeine at least 2 hours before the Test Day; (c) ensure they are
well hydrated; and (d) ensure that they are adequately fed by consuming a meal at least 2 hours before arrival to the Test Day. These factors aim to reduce the likelihood of malaise, gastrointestinal disturbances or heightened anxiety on the Test Day.

Compliance checks
Participants will complete a urinary drug screen (DrugCheck NxtStep Onsite Urine Test Cup, to identify any recent use of cannabis, ecstasy (MDMA), amphetamines, benzodiazepines and opioids) and, if they are female, a urine pregnancy screen, on arrival at the study site. The trial coordinator will also confirm compliance with the standardisation procedures and if there have been any changes to the participant’s health status or medication use since the last contact. Participants who meet these requirements will be randomised; those who do not may be invited to return at another time if suitable.

Experimental procedures
Following randomisation, participants will be fitted with the Equivital EQ02+ LifeMonitor belt and the VR headset. There will then be a 10 min collection of pretreatment measures (see the Study outcomes section). After this, the VR headset and Equivital EQ02+ LifeMonitor belt will be temporarily removed, the treatment administered and the participant given a compulsory standardised caloric beverage to consume; specifically, 500 mL of ‘Up & Go Liquid Breakfast’ (Sanitarium, Berkeley Vale, NSW, Australia) containing approximately 1640 kJ, 16.8 g of protein, 8.6 g of fat and 57 g of carbohydrates.

For consistency, all participants are required to consume this beverage in its entirety, which aims to potentiate the absorption of CBD in the gastrointestinal tract and provide participants with sustenance during the test session. Participants will be provided with a rest period of approximately 50 min, during which they will be left alone in a quiet reception area and encouraged to undertake some low-stress reading; this delay is aimed at allowing CBD plasma concentrations to approach a near-maximal level.16 Following this, participants will be provided with instructions on the three VR tasks and the functionality of the VR hardware during a 15 min ‘VR Orientation’ session. The VR headset and Equivital EQ02+ LifeMonitor belt will then be re-fitted for a 10 min collection of the pretask measures. The devices will remain fitted to participants until the end of the experimental procedure.

VR tasks
The three tasks developed for this clinical trial are the ‘Public Speaking’ task (for psychosocial stress), the ‘Walk the Plank’ task (for situational anxiety) and the ‘Rollercoaster Ride’ task (for motion sickness). Although these exact VR tasks have not been previously used in clinical trials or laboratory studies, similar tasks have been reported in the broader scientific literature.29 32 40–42 51

The 15 min ‘Public Speaking’ task was modelled on previous studies that found CBD to have anxiolytic effects during public speaking challenges23 24 39 and the Trier Social Stress Test (TSST).32 The above-mentioned public speaking tasks varied in their methodology and involved either ‘simulated’ public speaking tasks whereby participants delivered a speech in front of a video camera or real-life tasks where participants delivered speeches to a live audience.23 24 39 Conversely, the TSST is a structured stress paradigm involving a 10 min speech preparation period followed by a 10 min test period during which participants complete a 5 min job application speech followed by 5 min of mental arithmetic.53–55 In one study, a VR adaption of the TSST elicited similar salivary cortisol and subjective stress responses to a real-life TSST, demonstrating that the two were equivalent.29 The current study uses a modified VR version of the TSST involving a panel of virtual judges who withhold all feedback or affirmation (figure 2A).

The task involves a 3 min ‘speech preparation period’ (ie, ‘please mentally prepare a speech on what attributes and experience you have that makes you the ideal candidate for your dream role’) and a 10 min ‘test period’ consisting of (a) a 5 min speech delivery period (ie, ‘please deliver your speech and aim to speak for the full 5 min’) and (b) a 5 min mental arithmetic challenge (ie, ‘please calculate 2703–13’. From the result, please subtract 13

Figure 2  (A) The panel of virtual judges from the ‘Public Speaking’ task; (B) the roof of the building and plank from the ‘Walk the Plank’ task; and (C) the view from the seat of the ‘Rollercoaster Ride’ task.
The 5 min ‘Walk the Plank’ task requires participants to virtually walk across a narrow virtual plank between two skyscrapers. Participants will be advised that they have become stranded on the top of the building and are required to signal for help using the safety beacon placed at the opposite end of the plank. For this task, participants will walk up and down the length of the clinic room with their movement mapped to the virtual plank and guided by virtual boundaries, signifying a safe space (figure 2B). VR studies using a similar challenge provided realistic experiences that induce physiological markers of stress that are consistent with acute anxiety (ie, ‘situational anxiety’).40–42

The 5 min ‘Rollercoaster Ride’ task challenges participants to complete a virtual rollercoaster ride (figure 2C). Participants will remain seated throughout this task and can indicate if they would like to stop the task early. Similar VR tasks have been shown to induce motion sickness in participants.32 43 44  Motion sickness will be explored explicitly during the ‘Rollercoaster Ride’ task, while cybersickness will be explored during all three VR scenarios.

Post-trial procedures
After completing the final VR task, participants have a 10 min recovery period. After this, they will be queried on any AEs experienced (ie, ‘Have you experienced any unfavourable symptoms?’), what treatment do they think they received (ie, CBD or placebo), and what are their confidence estimates (ie, ‘How sure are you of your guess on which treatment you received?’). All participants will be provided with the contact details of the research team to self-report any AEs over the next 24 hours. The trial coordinator or research assistant will record all AE reports using a REDCap AE report form and communicate to the trial physician if required.

The occurrence of AEs will be discussed weekly with the trial physician. Furthermore, a blinded summary of AE reports will be emailed to the trial physician monthly, and the trial physician will indicate if the rate of AEs is unacceptably high. In the unlikely event of a severe adverse event (SAE), the trial physician and the PI will be immediately notified, and all SAEs will be reported to the trial sponsor and the HREC within 72 hours.

Data collection
A summary of the data collected during the CAPSTAN trial and time of collection is provided in figure 3.

Study outcomes
The primary outcome measures include:
► Self-reported stress ratings on a Visual Analogue Scale (VAS) (nervous 0–100).
► Self-reported nausea ratings on a VAS (nauseous 0–100).

The secondary outcome measures include:
► Salivary cortisol.
► Heart rate.
► Skin conductance.
► Vomiting or near-vomiting episodes.
► Self-reported anxiety ratings on VASs including:
  – (tense 0–100).
  – (calm 0–100).

Figure 3 Data collected during the Cannabidiol for Acute Psychosocial Stress and Nausea trial ‘Test Day’. AC, arithmetic challenge; IPS, instructions for the ‘Public Speaking’ task; IRR, instructions for the ‘Rollercoaster Ride’ task; IWP, instructions for the ‘Walk the Plank’ task; RRT, ‘Rollercoaster Ride’ task; SD, speech delivery; SP, speech preparation; WPT, ‘Walk the Plank’ task.
Salivary cortisol, testosterone and progesterone

During the experimental procedure, oral fluid samples will be collected from participants five times using Salivette collection tubes (Sarstedt AG and Co, Nümbrecht, Germany). These samples will be collected immediately before drug administration, before the first VR task, and after each VR task. Participants will be advised to open the Salivette tube, place the pad in their mouth for 2 min or until soaked with saliva, then return the pad to the tube and firmly seal it. The samples will be centrifuged for 2 min at 1000×g and analysed simultaneously for cortisol (a secondary outcome) and testosterone and progesterone (exploratory outcomes) using an in-house developed mass spectrometry method.

Heart rate

Heart rate will be measured for 10 min immediately before drug administration (baseline measurement), for 10 min at baseline and continuously throughout all three VR tasks using the EQ02+ LifeMonitor and belt, as described in previous studies. This is a wireless, medical-grade monitoring system that records a range of physiological measures (such as ECG, breathing rate, tri-axial acceleration, galvanic skin response, skin temperature) using a wearable vest and permits live data streaming and download using the LabChart software.

Skin conductance

Skin conductance will be measured for 10 min immediately before drug administration (baseline measurement), for 10 min at baseline and continuously throughout all three VR tasks.

Skin conductance of the forehead will be measured using the Equivital GSR Sensor connected to the EQ02+ LifeMonitor and belt. Skin conductance of the fingers will be measured using MLT117F/10 GSR finger electrodes connected to a FE116 GSR Amp with a PLCF1 front-end interface used with PowerLab C software (ADInstruments, Oxford, UK), a system used in previous studies. Research suggests that forehead skin conductance may correlate with motion sickness, while finger skin conductance correlates with acute stress. Therefore, both will be measured in the current study.

Vomiting episodes

The Test Day source document will record vomiting episodes (if any) throughout the experimental procedure.
Eye-tracking

Eye-tracking data will be collected continuously throughout the VR tasks using the VR headset. These measures will provide highly precise, objective data by which to examine participant’s compliance (frequency and duration of eye closing) and engagement and response (frequency and duration of gaze at areas of interest, that is, the panel of judges in the ‘Public Speaking’ task or the plank in the ‘Walk the Plank’ task) during the VR challenges.64 Gazing at predefined points of interest (eg, the judges in the ‘Public Speaking’ task or the plank in the ‘Walk the Plank’ task) is based on the ‘Eye-Mind Hypothesis’ that describes the tendency for people to direct their gaze towards what they are thinking about.64–66 Both eye closing and gaze away from points of interest may correlate to fear or avoidance behaviours.67

Data management

Participant information collected for this trial will be securely stored and treated as confidential. Participants’ identifying information will be anonymised using unique codes: initially, a screening number and, later, a randomisation number. The key to these codes will be securely stored in password-protected files inaccessible from the internet. Clinical trial data will be collected and managed using REDCap, a secure, online programme supported by the University of Sydney; access is password-protected and will only be available to approved research staff. Hard copies of patient data will be securely stored in locked filing cabinets at the study site. Only the study investigators have access to the participant data. All trial data will be stored securely for at least 15 years. The findings of this clinical trial will be disseminated via conferences, publications and media, as applicable. Participants will be informed of the results of the study at the conclusion of the trial. No participants will be identified in any report or publication of this study or its results.

Data and safety monitoring

Data monitoring will occur monthly for all new participant entries logged into the REDCap system; a designated team member will adhere to a standardised process of data review, raising queries and locking forms once the review has been completed. Safety monitoring of AEs will be managed according to sponsor and HREC requirements. As this is a small, single-centre, low risk, clinical trial using an acute, low-dose CBD, an independent data safety monitoring committee will not be formed. However, an independent ‘Expert Group’ has been formed and will be consulted by the research team and HREC in the unlikely instance of a SAE. The Expert Group comprises three research physicians with extensive experience with CBD clinical trials. The decision to terminate the trial lies with the PI based on safety data and recruitment targets.

Roles and responsibilities

The study investigators have led the design of this study and are responsible for the management and conduct of this clinical trial. The study investigators will conduct the analysis and will make all publication-related decisions.

Statistical methods

Sample size estimation

The target sample size was determined a priori using power calculation software (G*Power V.3.1.9.6, University of Kiel, Germany). In an earlier investigation, Linares et al23 found that 150 mg CBD decreased subjective ratings of anxiety on the Visual Analogue Mood Scale during a simulated public speaking test, although non-significantly (placebo: 18.6±15.9 mm; n=15; CBD: 7.6±15.5 mm; n=15; Cohen’s d=0.70).23

Using an equivalent effect size (Cohen’s d=0.70), a power (1−β) of 0.8 and a two-sided α=0.05, we estimate that n=68 participants will be required to detect a significant effect of CBD on anxiety. Clinical trials conducted by the Lambert Initiative for Cannabinoid Therapeutics have indicated participant retention of ≥90%.48 68 Therefore, the n=74 will be recruited to account for attrition.

Statistical analysis plan

The primary and secondary outcomes and eye-openness will be analysed using generalised linear mixed models (GLMM), while eye gaze will be analysed using a mixed-effects multinomial logistic regression. Treatment, time and the treatment×time interaction will be included as fixed effects, and the participant will be included as a random effect, with other covariates included as appropriate to improve goodness of fit (eg, sex, age, time of day). To refine the models, we will use corrected Akaike Information Criterion.69 We will calculate Δm between models and exclude models with Δm≥2 as having substantially less support.70 No covariance structure will be specified (unstructured). To identify the best distribution and link for the GLMM, the data type, residual plots, Shapiro-Wilk normality test, Levene’s test for homogeneity of variance and Pearson’s dispersion test will be used. Type III Wald χ² tests will be used to generate main effects p values. A priori planned uncorrected pairwise comparisons will be performed to compare:

- Subjective ratings of stress on a stress VAS (nervous 0–100) across treatments at (timepoint t=125 (SD), figure 3).
- Subjective ratings of stress on a stress VAS (nervous 0–100) across treatments at (timepoint t=147 (WPT), figure 3).
- Subjective ratings of nausea on a nausea VAS (nauseous 0–100) across treatments at (timepoint t=165, figure 3).
- Subjective ratings of nausea on a nausea VAS (nauseous 0–100) across treatments at (timepoint t=175, figure 3) as these are the primary outcome measures. Dunn-Šidák corrected pairwise comparisons will be performed where additional significant main and interaction effects are present. Statistical significance will be accepted as p<0.05. The statistical analysis plan will be...
finalised before the last participant Test Day and will be available on request.

Author affiliations
1The Lambert Initiative for Cannabinoid Therapeutics, The University of Sydney, Sydney, New South Wales, Australia
2The Brain and Mind Centre, The University of Sydney, Sydney, New South Wales, Australia
3Sydney Pharmacy School, The University of Sydney, Sydney, New South Wales, Australia
4School of Psychology, The University of Sydney, Sydney, New South Wales, Australia
5The Boden Initiative, Charles Perkins Centre, The University of Sydney, Sydney, New South Wales, Australia
6RPA Institute of Academic Surgery, Sydney Local Health District, Sydney, New South Wales, Australia
7Yellow Dog Man Studios s.r.o, Ostrava-Jihl–Zábrech, Czechia
8The Body Initiative, Sydney Local Health District, Sydney, New South Wales, Australia
9The Boden Initiative, Sydney Local Health District, Sydney, New South Wales, Australia
10The Lambert Initiative for Cannabinoid Therapeutics, Sydney Local Health District, Sydney, New South Wales, Australia
11The Lambert Initiative for Cannabinoid Therapeutics, The University of Sydney, Sydney, New South Wales, Australia
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