PROTOCOL

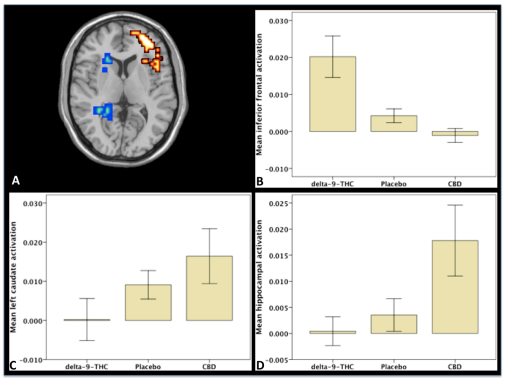
I. BACKGROUND:

While dopaminergic(*1-4*) and glutamatergic(*1-10*) neurotransmitter systems and their receptors have traditionally been investigated in the context of their role in psychosis, another receptor system that has not attracted as much attention from researchers until recently has been the endocannbinoid system. CB1 receptor, the main central cannabinoid receptor (*11*) is ubiquitous in distribution and plays a role in modulating the function of several neurotransmitters including dopamine and glutamate (*12*). A growing body of epidemiological studies have also linked regular frequent use of cannabis, as a risk factor for the development of schizophrenia (*13*). The main central molecular target for delta-9-THC, the major psychoactive ingredient in cannabis, responsible for its psychotogenic effects is the CB1 receptor, where it has a partial agonist effect (*12*). Evidence has also emerged of alterations in the endocannabinoid system in those with psychosis (*14-17*). However, the precise role of alterations of the endocannabinoid system in psychosis is unclear. One way to investigate the relationship between dynamic alterations of the endocannabinoid system and psychosis is to examine this under experimental conditions in individuals who are at ultra-high risk for psychosis following challenge with cannabinoids. Individuals at ultra high-risk of psychosis (UHR) experience brief or subclinical psychotic experiences that have been shown to predict the onset of schizophrenia and related psychotic disorders (*18-20*), with the largest naturalistic follow-up studies indicating that around 35% of subjects will develop a frank psychotic disorder, majority of them developing this within 2 years (*21, 22*). This population is an ideal group to investigate the neurobiological basis of psychosis and its relationship to endocanabinoid alterations. Although they are experiencing acute psychotic symptoms, they are usually naïve to antipsychotic medication, and are functionally intact and able to tolerate and cooperate with complex neuroimaging and other experimental investigations. In contrast, it is difficult to recruit patients with schizophrenia who have not already been exposed to antipsychotic medication, which would confound interpretation of data from studies involving administration of cannabinoids. However, because of the evidence linking cannabis use and delta-9-THC with increased risk for psychosis and psychotic symptoms respectively, it would be unethical to employ either cannabis or delta-9-THC as the challenge drug to perturb the endocannabinoid system. On the other hand, Cannabidiol, another cannabinoid that has attracted attention in recent years and is a non-psychoactive compound, may be an useful tool to safely modulate the endocannabinoid system in man. While delta-9-THC is a partial agonist at cannabinoid (CB1) receptors, recent data suggests that Cannabidiol may have an inverse agonist/antagonist effect at the same receptors, in addition to its various other possible mechanisms of action(*12*). Consistent with this, cannabidiol also has opposite symptomatic and neural effects to that of delta-9-THC. For example, using a repeated measure, within-subject, placebo-controlled design and combining fMRI and pharmacological challenge with the two main components of cannabis, delta-9-THC and Cannabidiol, we have found that delta-9-THC induced psychotic and anxiety symptoms in healthy individuals and that these effects were directly related to its effects on activation in the striatum during verbal learning (*23*) and attentional salience processing(*24*) and the amygdala during emotional (fear) processing (*24, 25*) tasks respectively. Cannabidiol had opposite effects to delta-9-THC on striatal and amygdala activation during the same cognitive tasks (*24, 25*) (Figure 1) in the same individuals, was well-tolerated, did not induce psychotic or anxiety symptoms and did not cause intoxication. Furthermore, in a separate pilot sample, employing a placebo-controlled design, we have shown that cannabidiol can block the induction of psychotic symptoms by delta-9-THC in healthy individuals (*25*). This is also consistent with independent evidence that Cannabidiol can block the symptomatic effects (*26, 27*) and neurocognitive impairments (*28-30*) caused by delta-9-THC (*26*). Consistent with human data, animal studies have also demonstrated that Cannabidiol may promote hippocampal neurogenesis (*31*) and rescue memory function both following acute and chronic administration (*32*) in animal models of cognitive impairment as well as have anti-aversive effects in animal models of anxiety(*33*). Also, a wealth of evidence exists regarding the safety of cannabidiol following acute and longer-term dosing in man(*34*). Thus cannabidiol is a safe, well-tolerated cannabinoid that may allow investigation of the effects of acute as well as short-term modulation of the endocannabinoid

system on the neural substrates for psychosis to understand the precise role of alterations in this system in schizophrenia.

In this study, we propose to examine the effects of acute as well as short-term modulation of the endocannabinoid system in the UHR subjects by employing an experimental design that combines pharmacological challenge with functional neuroimaging using a parallel-group, double-blind, randomized, placebo-control design.

Figure 1: Opposite effects of delta-9-THC and CBD relative to placebo on prefrontal, left caudate and hippocampal activation (BOLD response) during visual oddball salience processing. The left side of the brain is shown on the left side of the images.



II. OBJECTIVES:

The principal objective of this exploratory study is to investigate the precise relationship between dynamic alterations of the endocannabinoid system by administering CBD, an inverse agonist/ antagonist cannabinoid, and the functioning of the neural substrates for learning, salience and emotional processing that may underlie the psychotic and anxiety symptoms experienced by the UHR population. Furthermore, we propose to examine whether treatment with CBD is associated with an effect on plasma endocannabinoid [Anandamide, 2-Arachidonoylglycerol (2-AG), Palmitoyl-ethanolamine (PEA), Oleoyl-ethanolamine (OEA)] levels over the same time period.

III. METHODOLOGY:

We propose to employ complementary strategies to address the objectives of the study by examining the effects of CBD on different parameters of interest acutely and following steady-state dosing:
1) neurocognitive and neurochemical mechanisms for the symptomatic effects employing functional MRI and proton magnetic resonance spectroscopy (^{1}H-MRS)
2) effect on psychotic and anxiety symptoms following symptom-induction strategies, and
3) effect on endocannabinoid signaling by measuring plasma endocannbinoid levels.

Specifically, we propose to examine whether acute administration of CBD can modulate the neurocognitive and neurochemical substrates underlying psychotic and anxiety symptoms by examining the acute effect of CBD on neural activation during learning, salience and emotional (fear) processing tasks in UHR individuals with an at-risk mental state (ARMS) for psychosis. Furthermore, we propose to examine whether these acute effects persist or change in the short-term, after continued administration of CBD for 3 weeks, by examining the change in psychotic and anxiety symptom ratings and plasma endocannabinoid levels relative to baseline in the two treatment groups as well the effect on their neurocognitive and neurochemical substrates. Effects observed under steady-state conditions following 3 weeks treatment with CBD will confirm that the acute effects of CBD relative to placebo noticed on day 1 of the study are not non-specific effects unrelated to the perturbation of the endcannabinoid system.

Although the present study employs a double-blind, placebo-controlled, randomized design similar to a clinical trial, unlike in a clinical trial, the objective of the present study is to test both the acute effects as well as the non-acute effects of short-term modulation of the cannabinoid system using a pharmacological challenge strategy. Hence, we have decided to obtain the measurements at 2 different time-points: one for measuring the acute effects and another for non-acute short-term effects. Another rationale behind this approach is that this is a proof-of-concept, pilot study. Hence, the objective is to optimize the acquisition of usable and meaningful data and mitigate the potential risks related to attrition of study participants in a complex study of this nature. Ideally, for the purposes of this experimental approach where one is looking for a better understanding of the biology of the disease (especially putative causal role of the endocannabinoid system in psychosis) as well as signals that may inform 'go/ no-go' decisions regarding future studies, one would like to employ a design whereby it is possible to measure the effects of steady-state levels of the active compound on symptoms as well as the neural mechanisms underlying those symptoms at the earliest measurable time-point. At the same time, one would like to obtain evidence of effects over a period that resonates with clinical reality, given the chronicity of the condition. While data obtained at day 21 is likely to be particularly informative in terms of understanding the disease biology, we are also mindful that because of the design of the study (i.e., assessments over a 3-week period) and nature of illness in the participant population, drop-outs are likely to occur over the course of this study. Inclusion of outcome measures at 2 time-points would ensure that we would still have adequate and meaningful data consistent with the proof-of-concept nature of the study, even if there were significant numbers of drop-outs. While the day 1 measures would allow an early glimpse at the biology and help mitigate the risk of attrition, the day 21 measures would help separate any positive signals from noise.

Hypotheses: We will test the following hypotheses in humans:
1) Relative to the placebo condition, administration of CBD will acutely modulate medial temporal, striatal, midbrain, cingulate and prefrontal activation measured using fMRI (BOLD response) during learning, salience and emotional (fear) processing tasks in UHR individuals.
2) Relative to the placebo condition, administration of CBD will acutely modulate hippocampal glutamate levels (measured using ^{1}H-MRS) in UHR individuals.
3) Relative to the placebo treatment group, CBD treatment group will demonstrate a change in the medial temporal, striatal, midbrain, cingulate and prefrontal activation during learning, salience and emotional (fear) processing following 3 weeks of treatment in the UHR subjects.
4) Relative to the placebo treatment group, CBD treatment group will demonstrate a change in the hippocampal glutamate levels (indexed using ^{1}H-MRS) following 3 weeks of treatment in the UHR subjects.
5) Relative to the placebo treatment group, CBD treatment group will demonstrate a change in the severity of baseline UHR symptoms and endocannabinoid levels following 3 weeks of treatment and post-induction psychotic and anxiety symptoms following 1 and 3 weeks of treatment in the UHR subjects.

Subjects:
Inclusion criteria-

i) Forty right-handed UHR individuals (35) between 18- 35 years satisfying CAARMS criteria (36) will be recruited locally from OASIS (**www.oasislondon.com**), a large clinical service for this group.

ii) Most UHR subjects presenting to OASIS are medication-naïve, and only those who are naïve to antipsychotic medication will be included. Use of cannabis and other illicit substances will be assessed using a structured clinical interview(37).

Exclusion criteria- Include

i) history of previous psychotic disorder or manic episode,

ii) a current DSM IV diagnosis of substance dependence (except cannabis dependence),

iii) neurological disorders (eg., epilepsy) or severe intercurrent illness that may put the person at risk,

iv) IQ of less than 70,
v) female subject who is unwilling to use two forms of contraception (one of which must be a barrier contraception), pregnant, lactating or planning pregnancy during the course of the study and 3 months from the date of the last dose and a male subject whose partner is of child-bearing potential and unwilling to use a barrier method of contraception along with their partner.

Identification of participants- All patients under care of the early intervention services (OASIS team) who have expressed interest to their care-coordinator in taking part in the study and have agreed to be contacted will be contacted telephonically by study staff. If they express interest in taking part following brief telephonic explanation of the study, arrangement will be made for face-to-face meeting for detailed explanation of the study and for the purposes of giving study information sheet for the purposes of consenting. They would be further contacted after 1-2 days (at least 24 hours later) to arrange for a visit in case they were still interested. Written informed consent will be obtained on the day of the first study visit.

Design: Employing a parallel-group, double-blind design, subjects will be randomly allocated to one of two groups: 1) Cannabinoid challenge group and 2) placebo group. They will receive either 600 mg of CBD, a dose that has been employed with minimal side-effects such as mild drowsiness in healthy individuals(*25*) or placebo, administered once a day orally in identical capsules for 3 weeks. They will take part in experimental sessions under identical conditions on the first day as well as the last day (day 21) of the study, 2 hours after administration of the first dose of the drug. Outcome measures will be recorded and venous blood samples to monitor CBD levels will be obtained at various time-points (detailed below) on day 1 and day 21 (end of study) as well as on day 8 and day 15 of the study. Regular telephone contacts will be maintained over the first week of the study to ensure continued compliance and monitor side-effects.

Procedure and Measurements:

Measures:

Psychopathological ratings**:** Comprehensive assessment of at-risk mental states (CAARMS)(35, 36), State-trait Anxiety Inventory (STAI)(38);

Ratings of Functional status: Global assessment of functioning(39);

Compliance**:** pill count;

Tolerability**:** Assessed by self-report of side-effects and the UKU side-effect rating scale(40);

Safety bloods**:** Haematology (Full blood count and Haemoglobin) and Biochemistry (Urea & Electrolytes, liver function test, thyroid function test, lipid profile)**;**

Vital signs**:** Heart rate and Blood pressure;

Physical examination**.**

MRI scanning: fMRI data will be acquired using the 3T scanner at the Centre for Neuroimaging sciences at the Institute of Psychiatry, KCL, while participants perform a cognitive activation tasks (details below) inside the scanner.

Procedure on day 1 (online session**):** A urine drug screen for amphetamines, benzodiazepines, cocaine, opiates and THC will be performed on the day of the experimental session and the results recorded. Subjects will also be advised to refrain from using alcohol for 24 hours or nicotine for 6 hours on the day of scanning. Safety blood samples for (routine biochemistry and haematology) will be obtained and physical examination and vital signs recorded on all participants on day 1 before entering the study.

Baseline measures will be obtained and then psychopathological measures will be recorded at baseline before drug administration and 120 min, and 300 minutes after the administration of the drug using standard rating scales. CAARMS will be recorded only at baseline. Venous blood samples will be taken just before drug administration, and at 120 min (before entering the MRI scanner), and 300 minutes (after coming out of the MRI scanner) after drug administration to monitor CBD and plasma endocannbinoid levels on both the days. Blood pressure and heart rate will be measured at the same time points. Subjects will enter the MRI scanner at 180 min after administration of the drug, and will be scanned over a 90-minute period to obtain functional MRI

and ^{1}H MRS and arterial spin labelling (ASL) data. Previous work indicates that plasma levels of CBD remain stable over this period following oral administration.
Procedure on day 8: Compliance and Tolerability measures will be recorded on day 8 of the study. Venous blood samples to monitor CBD levels will be obtained and vitals signs monitored on these occasions. Safety bloods will be obtained on day 8 and psychopathological ratings will be obtained on day 15 of the study. Participants will also take part in symptom induction experiments.
Procedure on day 15**:** Compliance and Tolerability measures will be recorded. Venous blood samples to monitor CBD levels will be obtained and vital signs monitored on these occasions..
Procedure on day 21 (online and offline session**):** A urine drug screen for amphetamines, benzodiazepines, cocaine, opiates and THC will be performed on the day of the experimental session and recorded. Subjects will also be advised to refrain from using alcohol for 24 hours or nicotine for 6 hours on the day of scanning. Safety blood samples for (routine biochemistry and haematology) will be obtained and physical examination and vital signs recorded on all participants.
Psychopathological measures will be recorded at baseline before drug administration and 120 min, and 300 minutes after the administration of the drug using standard rating scales. CAARMS will be recorded only at baseline. Venous blood samples will be taken just before drug administration, and at 120 min (before entering the MRI scanner) and 300 minutes (after coming out of the MRI scanner) after drug administration to monitor CBD and plasma endocannbinoid levels on both the days. Blood pressure and heart rate will be measured at the same time points. Subjects will enter the MRI scanner at 180 min after administration of the drug, and will be scanned over a 90-minute period to obtain functional MRI and ^{1}H MRS and ASL data. Previous work indicates that plasma levels of CBD remain stable over this period following oral administration. Participants will take part in offline symptom-induction experiments after completion of MRI scanning.

End of study measures**:** In addition to psychopathological ratings and blood samples for CBD levels, that will be obtained on day 21 as described earlier, additional measures will be obtained for function, compliance and tolerability (as detailed earlier). A physical examination will be conducted at the end of the study.

Cognitive Tasks to be performed during scanning
All of these paradigms are well-established and have been used extensively in previous fMRI studies with CBD (*23-25*).
1. VERBAL PAIRED ASSOCIATES TASK (VERBAL MEMORY)*(23)* - In an Encoding condition, subjects will be shown word pairs and asked to say ('yes' or 'no') if the words 'go together'. In a subsequent Retrieval condition they are shown one from each pair and asked to say the word that it was previously paired with. Stimuli are presented every 5 s in alternating blocks of 8 pairs and verbal responses will be recorded on-line.
2. 'MONETARY INCENTIVE DELAY' (MID) task (41) - the subject is presented with 'cue' images followed by a white rectangle. They have to press a button as quickly as possible when they see the rectangle. The participants initially start with a fixed quantity of virtual 'winnings' in pounds sterling, which they can then win or lose depending on response time. Each trial lasts 6 seconds including 'feedback' for 1.65 seconds stating how much they have won or lost. There are 2x10 minute sessions consisting of 72 trials, and the subject is paid the cumulative winnings in cash at the end of the day (but not charged for losses).
3. EMOTIONAL (FEAR) PROCESSING TASK(*25*)- Subjects will be presented with a series of 10 different facial identities, each expressing either a 50% (mildly fearful) or 100% (prototypically fearful) intensity of fear, or a neutral expression. They will be asked to indicate the gender of each face by pressing one of two buttons**.** Thirty different facial stimuli will be presented twice each for 2 seconds with the order of facial identities and expression type pseudo-randomized such that the same identity or facial expression type will not be presented successively.

Offline symptom-induction experiments

a) ANXIETY SYMPTOM: Trier Social Stress Test (TSST) (42). The subject is given 10 minutes to prepare a 5 minute speech and to perform an arithmetic task for a job interview and told to imagine that the interview is for their dream job. They are informed that 2 professional interviewers will be observing for 'signs of extroversion' while recording their

verbal and non-verbal performance on camera for later analysis. After 5 minutes they are asked to perform an arithmetic task during the interview. The interview itself lasts 10 minutes, and the whole process takes 20 minutes in total. The experience is designed to stimulate anxiety, and no information regarding 'extroversion' or arithmetic performance is recorded (the camera is fake). During consenting, the subject is informed that the interview is artificial and solely for research, they are de-briefed following the second interview and again reminded that the entire experience is false and purely for symptom induction. Visual-analogue mood scales (for anxiety) and the self-statement-scale-during-public-speaking (SSDPS) and state-social-paranoia-scale (SSPS) will be administered over the course of the task and venous blood samples for cortisol analysis will be taken. This task has been shown to result in transient increase in cortisol and in the severity of anxiety symptoms and to be senstitive to the effects of CBD(43).

b) PSYCHOTIC SYMPTOM (PARANOIA)(44, 45): In this task, participants are asked to wear a Virtual Reality (VR)-headset which simulates a 4-minute journey on the Underground subway. Ambient sounds, conversations, gazes, movements and interactions are simulated. The setting/interactions are deemed 'neutral' by controls, thus any paranoid thinking or suspiciousness is unfounded. The VR experience has been employed in UHR population at our centre and has been popular with participants(46). In earlier experiments, over 60% of PsP participants [n=63] reported transient paranoid and referential thinking in this setting and provide notably high scores on the state-social-paranoia-scale (SSPS) which we will administer before and after the task and venous blood samples for cortisol analysis will be taken. In these previous experiments, increase in the paranoid and referential thinking within the VR set-up did not persist beyond the experimental session and none of the participants required rescue medications or supportive psychological treatment as a result.

Image Acquisition: Echo-planar images depicted blood oxygen level-dependent (BOLD) contrast will be acquired on a General Electric (Milwaukee, USA) 3T HDx MR system at the Institute of Psychiatry, London. During the verbal paired associates task, acquisition will be compressed to allow the processing of auditory/ verbal stimuli in silence.

STATISTICAL ANALYSIS:

Study endpoints:

Primary outcome- There are two sets of primary outcomes for this study, measured at day 1 and at day 21, in order to account for the specific design.

Day 1-

i) fMRI BOLD signal in the hippocampus, striatum and amygdala measured during the memory, MID and emotional (fear) processing tasks on day 1.

Day 21-

ii) Change in fMRI BOLD signal in the hippocampus, striatum and amygdala measured during the memory, MID and emotional (fear) processing tasks on day 21 relative to that obtained on day 1.

Secondary outcome-

Day 8-

i) Severity of psychotic (measured using SSPS scale) and anxiety (measured using STAI) symptoms following symptom induction strategies on day 8 of the study.

Day 21-

ii) Change in plasma endocannabinoid (Anandamide, 2-AG, OEA, PEA) levels measured following administration (and before getting inside the scanner) of the last dose of the drug on day 21 relative to that obtained immediately before drug administration on day 1 of the study.

iii) Severity of psychotic (measured using CAARMS total score) and anxiety (measured using STAI) symptoms measured following administration of the last dose of the drug (before getting inside the scanner) relative to that obtained immediately before administration of the first dose of the drug on day 1.

iv) Change in severity of psychotic (measured using SSPS) and anxiety (measured using STAI) symptoms following symptom induction strategies measured on day 21 relative to that measured on day 1 of the study.

Analysis of behavioural and physiological data: Repeated measures ANOVA (SPSS version 16) will be used to analyse performance during the cognitive paradigms, psychopathological and side-effect ratings and plasma endocannabinoid levels with drug manipulation (placebo / CBD) and time as the factors.
Image analysis: Images will be processed then analysed employing non-parametric approach (XBAM version 4; **www.brainmap.co.uk**). Prof Michael Brammer, one of the developers of the XBAM image analysis package and a collaborator will advise on the statistical aspects of the study. For each paradigm, we will examine the main effect of task and the task x drug interactions.
Power Calculation: As this is a proof-of-concept, pilot study, no formal sample size calculation has been performed. The objective of the specific funding stream from the MRC (UK) that has funded this project (Experimental Medicine call for Mental health) is to look for early signals that can then help in making decisions regarding funding further definitive studies. Hence, although we have included a section for power calculation in the protocol, this is based only on neuroimaging (fMRI) evidence in healthy volunteers, as similar data does not exist in this patient population. Based on our previous study in healthy volunteers using a repeated-measures, within-subject design, a sample size of n=15 would be required to detect differences between the placebo and CBD condition on neural activation with an alpha (α) of 0.05 at 90% power and an SD of 0.04 and anticipated minimal difference in means as 0.036(*25*). Thus, a sample of n=40 as proposed in the present study is likely to be sufficient to obtain early evidence of effect of CBD on neural activation measures.
IV. MILESTONES: We plan to recruit 2-3 subjects a month into the study and estimate completion of recruitment within 1.5 years. Data analysis and drafting of report will be complete over the last 6 months.
V. ETHICS, GOVERNANCE & DATA PROTECTION: Safety and Ethical issues: Only subjects who have previously used cannabis and who have not experienced any adverse effects will be asked to participate. Pharmacological grade CBD will be administered to study participants. In our previous work, 600 mg of oral CBD was found to be safe in healthy individuals and in collaborative work, 5 mg of IV Cannabidiol blocked the symptomatic effects of THC without having any adverse effects itself (25). Published human studies have administered CBD for varying durations including over 3 weeks (the duration proposed for the present study) in doses ranging from 150-1500 mg/day in studies (26, 34, 47) involving healthy volunteers and those with psychiatric and neurological conditions without any adverse effects. At the end of testing, we will ensure that subjects are entirely well, instruct them not to drive or operate machinery for 12 hours and they will be transported home by taxi. Although in previous experiments, increase in psychotic symptoms (such as paranoid and referential thinking) within the VR set-up did not persist beyond the experimental session and none of the participants required rescue medications or supportive psychological treatment as a result, a trained psychiatrist with access to medications and a psychologist would be available to provide medical and psychotherapeutic support if needed. Furthermore, nursing support would be available at the clinical research facility in case of need. Participants who are unable to tolerate any aspects of the protocol will be withdrawn from the study.
Data protection: The study will be conducted in compliance with the relevant UK directive (Data Protection Act, 1998) and information relating to participants collected for the study will be kept confidential and secure, with the participants identified by a code. An appropriate case report form (CRF) that will comprise spreadsheets to store data electronically will be used for this study, with access restricted to study personnel and level of access set to maintain privacy and confidentiality of participant information. All hardcopy data and source files will be stored in limited access facilities (locked cupboards) accessible only to study staff inside locked premises at the Department of Psychosis Studies, Institute of Psychiatry, London, UK.
An appropriate case report form (CRF) will be used for this study. The proposed CRF for each study participant would be an anonymised electronic document comprising spreadsheets to store data captured on the various study rating instruments. These CRFs would be maintained in an electronic database stored in a computer located within secure access facilities within the Department of Psychosis Studies, Institute of Psychiatry. Access to the CRFs and electronic database would be password protected and would be monitored and available to only study

personnel and anybody that may require access for regulatory reasons. The level of access would be set to maintain the privacy and confidentiality of participant information. Source documentation (a 'Source File' including information that may be documented in the patient's medical record) that substantiates the information collected in the CRF would be maintained for at least 20 years and longer if required by local regulations (other study-related documentation as outlined in the Good Clinical Practice guideline would also need to be retained for the same period of time). The CRF will be managed by staff involved in the study. Study participants would not be identified by name in the CRF where anonymised information will be recorded.

Withdrawal criteria: In accordance with the Helsinki declaration and other applicable regulations, study participants will have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care. Additionally, participants who experience adverse events (AE; including clinically significant laboratory result), which in the opinion of the investigator would compromise the continued safe participation of the subject in the study or who experience serious adverse events will be withdrawn from the study.
Exit criteria: UHR subjects who experience progression to a first episode of psychosis (operationalized using severity thresholds proposed by Morrison and colleagues(48): score of ≥ 4 on hallucinations or delusions or ≥ 5 on conceptual disorganization) will exit from the study. Clinical team involved in the care of the participant will be informed and a referral will also be made to the locality first-episode psychosis team.
Medication Supply, Storage and Randomisation: Study medications would be obtained from THC-Pharm (Frankfurt, Germany). All Study medications (both active drug and placebo) would be manufactured, packaged, labelled and supplied by STI pharmaceuticals according to GMP guidelines. Study medications would be stored at the Maudsley hospital pharmacy. Randomization of participants into the two treatment groups and blinding would be carried out by an experienced pharmacist at the Maudsley hospital pharmacy.

VI. DATA PRESERVATION FOR SHARING: The study data will be collected in an appropriate eCRF in an anonymised format, which along with source data will be stored for 20 years or longer.

VII. POTENTIAL BENEFITS/ IMPLICATIONS: This study will help clarify the role of the endocannabinoid system in psychotic disorders and may help identify novel candidate pathways/ molecules as targets for drug discovery.

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