PROTOCOL

Date: July 27, 2023

NCT #: 03787628

Title of Study: Cannabidiol Effects on Craving and Relapse Prevention in Opioid Use Disorder

Name of Sponsor/Company: University of California at Los Angeles (UCLA)

Name of Investigational Product: ATL5 softgel capsules (10% CBD)

Name of Active Ingredient: Cannabidiol

Study Center: Tarzana Treatment Center

All test procedures involving human subjects will be conducted only at this site in the U.S. Data analysis will be conducted at the Jane and Terry Semel Institute, David Geffen School of Medicine, UCLA

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Site Co-Investigators: Richard De La Garza, II, Ph.D.

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Phase of Development: Phase 2

INTRODUCTION

Opioid Use Disorder (OUD), involving prescription opioids or heroin, is a public health emergency leading to unprecedented drug-related mortality in the United States,[1-3] underscoring the need for innovative medical treatments for OUD. Several mediations are available for treatment of OUD. Of the opioid agonists, used, buprenorphine has a more favorable safety profile than methadone, but retention in treatment is low for both medications.[4,5] The opioid receptor antagonist naltrexone is also used for patients with OUD, but it has even lower adherence.[5]

Positive findings from preclinical and clinical studies provide a rationale for the use of cannabidiol (CBD) in the clinical trial proposed here. In animal models, CBD has behavioral effects suggesting that CBD may offer benefit in relapse prevention for patients with OUD. These effects include the attenuation of opioid reward and conditioned reinstatement of opioid-seeking behavior, stress-induced drug-seeking and reductions in anxiety- and impulsivity-like behaviors.[6,7] Moreover, a Phase 2, randomized, double-blind, placebo-controlled, pilot study found that a single dose of CBD (400 or 800 mg) decreased cue-induced opioid craving and blunted anxiety.[8,9]

Although promising findings suggest that CBD can reduce craving and anxiety, and attenuate opioid-related reward, rigorous clinical trials are needed to establish the full potential and determine the optimal dosage of CBD as adjunctive therapy for OUD. This is the background and rationale for the proposed study. Success in this project can reduce opioid–related deaths by providing a medication that will prevent relapse to opioid use, which puts individuals with OUD at risk for death from an opioid overdose.

STUDY OBJECTIVES

The overall goal of the proposed work is to perform a study on the effects of ATL5 in patients with OUD, receiving medication-assisted treatment with buprenorphine (transmucosal formulations, e.g., buprenorphine + naloxone) or methadone. ATL5 is CBD, extracted from hemp, at a 10% strength (softgel capsules with 100 mg/ml of CBD per capsule).

Primary Objective: To evaluate the safety and tolerability of CBD (600 mg/day) and its pharmacokinetic interaction with buprenorphine metabolism in the study population.

Based on prior work, CBD is expected to be well-tolerated and safe in patients with OUD[8,9], but safety signals (vital signs and laboratory test results) will be assessed. Because CBD inhibits cytochrome P450 isozymes including CYP3A,[10] which is the primary mechanism for hepatic buprenorphine N-dealkylation,[11] we will evaluate whether CBD poses potential safety concerns associated with buprenorphine or methadone treatment. We will seek to understand the drug-drug interaction for safe and effective treatment of OUD and to identify an optimal adjunctive dose of CBD for patients receiving buprenorphine or methadone treatment. We predict a drug-drug interaction between CBD and buprenorphine, whereby CBD will inhibit buprenorphine metabolism and increase the buprenorphine/norbuprenorphine concentration ratio. [Note: Intestinal and hepatic CYP3A activity only slightly affect human methadone N –demethylation.]

Secondary Objective: To determine the extent to which CBD (600 mg/day) reduces cue- induced craving for opioids.

CBD is expected to reduce cue-induced opioid craving (secondary outcome). Other outcomes are also expected to be affected: spontaneous craving and negative affect.

METHODOLOGY

General Experimental Design: This will be a randomized, double-blind, placebo-controlled study of ATL5 (CBD) (600 mg/day, [300 mg twice daily]) as adjunctive therapy to buprenorphine or methadone for patients with OUD, who are receiving inpatient behavioral therapy, including cognitive behavioral therapy.

Endpoints: The primary endpoint will be safety and tolerability of CBD in these patients, and it will be assessed via measurement of adverse events. Pharmacokinetic analyses will evaluate potential drug-drug interactions of CBD with buprenorphine metabolism. The secondary outcome measure will be cue-induced craving for opioids, assessed using the Desires for Drug Questionnaire (DDQ)[16] in the context of an opioid cue-induction paradigm in the laboratory session before CBD dosing on Day 0 (baseline without CBD) to scores on Days 7 and 28 (after adjunctive treatment with CBD) (*see Criteria for Evaluation below).*

Other Outcome Measures:

- spontaneous opioid craving, assessed using the Penn Alcohol-Craving Scale, as modified to assess opioid craving[17]
- affect, assessed using the Positive and Negative Affect Schedule (PANAS)[18]
- anxiety assessed by State subscale of the Spielberger State-Trait Anxiety Inventory[19]
- blood pressure, heart rate, and respiratory rate during the laboratory sessions
- Plasma levels of CBD
- plasma levels of buprenorphine

Participant Recruitment: Patients will be recruited from the Tarzana Treatment Center in the San Fernando Valley (TTC), where buprenorphine or methadone (as part of their treatment) and CBD (as part of this protocol) will be administered.[a] Tarzana Treatment Centers, Inc. is a community-based, private non- profit behavioral healthcare organization located in Southern California with several agency sites, including the one in the San Fernando Valley, where this protocol will be conducted.

TTC delivers drug and alcohol use treatment, has been accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) since 1987, and has a workforce that includes physicians, psychologists, and nurses. TTC's substance use treatment approach includes residential programs that are overseen by a Program Director and are staffed by a clinical supervisor, operations supervisor, counselors, interns, nursing staff and 24/7 technicians. Groups and services include education group, process group, 12-step, family group, mental health services and recreation skills. Cognitive-behavioral treatment is used in both individual and group therapy to address craving and relapse issues and in the treatment of mental health problems.

Randomization to Treatment: Up to 60 patients who meet all eligibility criteria will be randomized to receive CBD or placebo (up to 30 patients per group): CBD 600 mg/day (300 mg twice daily). Within each cohort, patients will be randomized by baseline plasma buprenorphine level (either below or ≥ 2 ng/mL)

Dosing and Testing Schedule: The study will comprise three periods: a 14-day screening period while patients are stabilized on buprenorphine), a 28-day treatment period (CBD 600 mg/day or placebo), and a 28-day follow-up period after termination of treatment with medication.

Laboratory sessions using a craving cue-induction paradigm will be conducted before dosing on Day 0 (baseline) and on Days 7 and 28 after adjunctive treatment with CBD.
Note: Participants will all be maintained on buprenorphine or methadone, which are robust, effective treatment for OUD that diminish cravings, and helps to protect participants if relapse occurs. Thus, conducting cue reactivity tests in the presence of opioid agonist medication is inherently less risky than in individuals with untreated OUD. Total scores > 70 on the Desire for Drug Questionnaire (scores ranging from 14 to 98) will be reassessed after participants remain in study visit area for 15 min and again at 30 min if the score remains above 70. Research staff will check in with participants to provide support and resources as requested, or to coordinate care with current clinical staff at TTC.

Adherence to medication in the trial will be assured as the patient will take the test medication (CBD or placebo) under supervision. Blood samples will be collected to determine plasma concentrations of CBD and its metabolites (7-hydroxy CBD and 7-carboxy CBD), buprenorphine and methadone and their metabolites as well as the endocannabinoids anandamide and 2-AG, which may contribute to the response to CBD and laboratory assessments of safety. Retention in treatment (this trial plus buprenorphine + naloxone) will be assessed over the 28-day medication (CBD or placebo) treatment period and weekly follow-up assessments for the subsequent month (28-day follow-up period).

Duration of Treatment and Dropout. Duration of inpatient treatment with buprenorphine or methadone (outside the scope of this protocol) is generally for about one month at the Tarzana Treatment Center (TTC), and buprenorphine or methadone is often continued after a client leaves TTC. The treatment phase of this study of CBD vs. placebo is 28 days. If a participant decides to stop taking buprenorphine or methadone and/or leave TTC before completing the 28-day intervention described in this protocol, they will be withdrawn from the study and will receive compensation for the portion of the study that they completed.

Number of Patients Planned: Approximately up to 60 patients will be recruited.

- The active treatment group will include up to 30 patients receiving CBD (600 mg/day).
- The control group will include up to 30 patients receiving placebo.

[a] Because buprenorphine or methadone will not be administered as a study medication and will be managed by the participant's X-waivered prescriber, study personnel will not directly adjust doses of these medications if participants endorse withdrawal or craving symptoms. However, with participants' consent, we will attempt to communicate this info to the participant's clinician for consideration of dose adjustment.

Diagnosis and Main Criteria for Inclusion (see Table 1 below): Patients will be 21-65 years of age and will meet criteria for current (over the 3 months before enrollment) OUD on the basis of the Mini International Neuropsychiatric Interview (MINI) 7.0.2 for DSM-5. They will have reported opioid use in the 60 days before evaluation and will be receiving a stable maintenance dose of ≥12 mg buprenorphine in a formulation including naloxone (buprenorphine/naloxone ratio of 4/1) or without naloxone or methadone for at least 7 days at the same maintenance dose.

When administered via the sublingual route, buprenorphine-naloxone is a safe and effective treatment for OUD that has a high therapeutic index and a ceiling effect for respiratory depression that reduces the likelihood of adverse outcomes. A buprenorphine dose range of ≥12 mg daily is a usual dosage for residents at the TTC and was selected to produce substantial occupancy of mu- opioid receptors. A 16-mg buprenorphine maintenance dose significantly decreases whole-brain mu- opioid receptor availability by 80 ± 2% relative to placebo, with nonsignificant increases in receptor occupancy by 32 mg of buprenorphine.[20] Occupancy of mu opioid receptors by buprenorphine correlates well with plasma levels of the medication and with questionnaire-based opioid withdrawal symptoms and attenuation of response to hydromorphone.[21]

Key Exclusion Criteria (see Table 2 below):

Table 1. Inclusion criteria
• Ability to read and speak English and has provided written informed consent.
• Age of 18-65 years (inclusive).
• Meeting criteria for an OUD according to the MINI for ≥ 3 months before screening.
• Self-report of opioid use in the 30 days before screening; verified by treatment center records.
• On a stable dose of ≥12 mg buprenorphine, either alone, or in combination with naloxone (buprenorphine/naloxone ratio of 4/1) or methadone for at least 7 days prior to staring and for the duration of the treatment phase of the study.
• If female, being surgically sterile or willing to use birth control (e.g., oral contraceptives, condoms, intrauterine device) or willingness to abstain from sex throughout the study.
• Body Mass Index (BMI) between 17.5 and 35 kg/m^2; total body weight > 110 lb (50 kg).
• Currently in residential treatment at the Tarzana Treatment Center.

Patients will be excluded for physiological dependence on alcohol or a sedative-hypnotic drug, requiring medical detoxification, receiving medication-assisted treatment with naltrexone, and showing signs of acute opioid withdrawal symptoms (score of 5 on the Clinical Opiate Withdrawal Scale, COWS).

Because Cue-induced craving for opioids will be a secondary outcome, participants will be screened to eliminate those who do not report sufficient craving in response to visual cues (pictures). Those who do not have a craving score of at least 50 (on a visual analogue scale with a maximum score of 100) for at least one image within one category (groups of images may be separated into smoking cues, pills and bottles, and injection paraphernalia). For example, for injection cues, a picture of a needle and syringe may elicit a craving response, though other images in the same group (i.e., picture of arm with vein bulging) do not elicit craving.

Exclusion criteria also include clinically significant medical conditions; and AIDS or current HIV seropositivity (as HIV positive individuals entering the Tarzana Treatment Center generally have medication treatment with antiviral and/or non-antiviral therapies that have potential interactions with CBD). Pregnancy and lactation also will be exclusion criteria. Because of evidence that CBD affects ovarian function, women with hormone values outside the normal range on a test battery will be evaluated with ultrasound; those who have evidence of ovarian suppression will be excluded.

Screening labs/tests will include direct bilirubin (D Bili) and liver function tests (LFT), baseline ECG, and pregnancy test for women. Parameters for exclusion include:

a. AST or ALT greater than or equal to 3Xs ULN.
b. Bilirubin greater than or equal to 1.5 Xs ULN.
c. Clinically significant abnormalities on EKG

d. Pregnancy test positive.

Based on Epidiolex® (CBD oral solution) label section 7, "Drug Interactions", we will exclude participants who are taking the following medications: strong a) inducers of CYP3A4 or CYP2C19 (e.g., rifampin, due to the potential to decrease CBD plasma levels); and b) substrates of UGT1A9 (e.g., diflunisal, propofol, fenofibrate), UGT2B7 (e.g., gemfibrozil, lamotrigine, morphine, lorazepam), CYP2B6 (e.g., bupropion, efavirenz), CYP2C19 (e.g., clobazam, diazepam) due to potential to inhibition of enzyme activity by CBD).

Table 2. Exclusion Criteria
• History of sensitivity to a CBD product or any of the ingredients in the study drug, including glycerin or gelatin.
• A condition that may affect drug absorption (e.g., gastrectomy).
• Taking a medication that has clinically significant interactions with CBD or are contraindicated for the study (check with study physician).
• Positive urine test for THC at screening. • Self-report of using CBD at screening. • PK analysis at screening showing evidence of CBD use (any level > 0).
• Physiological dependence on alcohol or a sedative-hypnotic benzodiazepine drug.
• Current medication-assisted treatment with naltrexone.
• Acute opioid withdrawal symptoms, as defined by a score on the COWS > 4. .
• Clinical laboratory finding of AST or ALT ≥ 3 times the upper limit of normal (ULN) or bilirubin > 1.5 times ULN.
• AIDS or HIV positive status (because treatment medications have potential interactions with CBD).
• Pregnancy or lactation.
• Clinically significant EKG abnormalities, as determined by the study physician, including the following: QTc >450 msec (men) or >470 (women) or QRS interval >120 msec (If QTc or QRS interval exceed these cutoff points, EKG will be repeated twice and the average of the three QTc values used to determine eligibility.), congenital long QT syndrome, history of prolonged QT in the 3 months before screening, corrected QT interval (Fridericia's – QTcF) >450 msec (male) or >470 msec (female) or history of risk factors for Torsades de Pointes.
• For women: any value outside reference ranges on a hormonal battery [estradiol, follicle-stimulating hormone, free thyroxine index, luteinizing hormone, prolactin, T3 uptake, thyroid-stimulating hormone, and thyroxine], followed by an abnormal ovarian ultrasound finding.
• Clinically significant cardiovascular, hematologic, hepatic, renal, or endocrine abnormalities, as determined by the study physician.
• Meeting criteria on the MINI for schizophrenia, Bipolar I disorder, psychotic disorder, having active suicidal ideation, or suicide attempt in the past 12 months. Or, answers "yes" to questions 4 or 5 on C-SSRS. NOTE: Participants with other psychiatric conditions, such as major depression, generalized anxiety, dysthymia, social phobia or specific phobia may be enrolled in the study if they are clinically stable.
• On the cue-induced opiate craving task at screening, the participant does not have a score of at least 50 (on a visual analogue scale with a maximum score of 100) for at least one image within one category. Note: Groups of images may be separated into smoking cues, pills and bottles, and injection paraphernalia. For example, for injection cues, a picture of a needle and syringe may elicit a craving response, though other images in the same group (i.e., picture of arm with vein bulging) do not elicit craving.

Investigational Product and Mode of Administration: ATL5, which is CBD, extracted from hemp, at a 10% strength (softgel capsules with 100 mg/ml of CBD per capsule) or matching placebo. The formulation that was selected for this clinical trial contains CBD and excipients as here:

a) emulsifying agents: Cremophor EL (Polyoxyl 35 castor oil), Tween 80 (Polysorbate 80), Plurol® Oleique (polyglyceryl-3 dioleate);
b) cwe o-surfactant: propylene glycol;
c) oil: Labrosol® (caprylocapryol polyoxyl-8 glycerides), medium chain triglycerides;
d) antioxidant: BHT (butylated hydroxytoluene).

ATL5 Softgel Capsules will be manufactured by Baxco Pharmaceutical Inc., (California, USA) under cGMP conditions. They will be administered orally as indicated below.

Dosage and Duration of Treatment: The planned study will evaluate ATL5 (300 mg, BID). The treatment period with CBD or placebo will be 28 days. Participants will be in the study for up to 10 weeks, including follow-up evaluation after completion of the 28-day treatment period.

Dose Justification: CBD will be tested at 600 mg daily. This dose was selected on the basis of safety data from human studies. In a previous clinical trial, doses of CBD as high as 50 mg/kg (i.e., 350 mg for a 70-kg participant) were well tolerated.[22] Doses between 300 and 1500 mg have been used in humans without toxicity or serious adverse events.[23-29] Forty-two subjects received 200 mg of CBD four times daily (total 800 mg per day) for 2 to 4 weeks to treat schizophrenia without notable side effects.[30] A review of 132 reports, which included animal and human studies, concluded that CBD was well-tolerated in humans, at doses of up to 1500 mg/day[31]fo

Sixty subjects were dosed to date in a pediatric pharmacokinetic trial with doses ranging from 10 mg/kg/day up to 40 mg/kg/day[32]; these doses were generally well tolerated, and no clinically significant safety concerns were identified, even in adolescents. In addition, 24 adults received doses of 20 mg/kg CBD (up to ~2000 mg as a single dose) (INS011-15-043) in a study evaluating the effects of food (fasting and a high-fat meal) on absorption of CBD. In that study, and in another that evaluated food effects on CBD absorption in 8 healthy adults (INS011-16-093), there were no safety issues and very few adverse events.

In a study of heroin-abstinent patients with OUD, 400 mg and 800 mg CBD were shown to be safe and well-tolerated when given with intravenous fentanyl.[33] Specifically, Systematic Assessment for Treatment Emergent Events (SAFTEE) data were similar between CBD dose groups, and there was no respiratory depression and no cardiovascular complications during any test session. However, no study has yet evaluated the effect of CBD as an adjunctive therapy to buprenorphine or methadone. Given the known safety and efficacy of CBD, we will compare CBD to placebo to determine whether CBD reduces cue- induced craving for opioids (primary outcome measure) and has other effects, such as relapse prevention in patients with OUD when used as an adjunctive therapy to buprenorphine or methadone.

Reference Therapy, Dosage, and Mode of Administration: The reference therapy will be placebo, consisting of softgel capsules that match the active test medication in appearance. The placebo softgel capsule formulation is composed of polyoxyl 35 polysorbate 80, plurol- oleique CC 497, propylene glycol, caprylocapryol polyoxyl-8 glycerides, medium chain triglycerides and BHT, in the same relative proportions as the ATL5 Softgel Capsules. The softgel shell will be composed of caramel color, gelatin, glycerin and purified water.

This formulation also will be manufactured by Baxco Pharmaceutical Inc. under cGMP conditions.

Safety Assessments and Monitoring: The following tests and procedures will be performed for safety monitoring throughout the study.

a. Comprehensive metabolic panel, CBC with differential, and urinalysis
   Key tests: AST, ALT and INR levels
   Sampling times: Days -7 to 0 (screening), Days 7, 14, 21 and 28 (treatment), and Days 35, 42, 49 and 56 (follow-up).
b. Assessment of Sedation
   Instruments and measures: Observed Observer's Assessment of Alertness/Sedation Scale (OAAS) and pulse oximetry
   Assessment times: Days -7 to 0 (screening), and Days 1-28 (treatment), and Days 29, 30, 31, 33, 35, 42, 49 and 56 (follow up).
c. Electrocardiogram
   Safety parameters: evidence of arrhythmia, recent MI, and 3rd degree heart block

Assessment times: Days -7 to 0 (screening) and Day 28 (treatment).

d. Ovarian hormone battery
   Hormone assays: estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, T3 uptake (THBR), thyroid-stimulating hormone (TSH), thyroxine (T4).
   If abnormality is seen, ultrasound will be obtained.
   Assessment times: Days -7 to 0 (screening), Days 7, 14, 21, and 28 (treatment), and Days 35, 42, 49 and 56 (follow up).
e. Suicidality
   Assessment: Columbia Suicide Severity Rating Scale (C-SSRS)
   Assessment times: Days -7 to 0 (screening), and Days 7, 14, 21, and 28 (treatment).

Interventions and Stopping Criteria:

a. Dosing will be stopped for slowed respiration and hypoxia (O2 saturation <94% on room air for 2 consecutive days with evidence of no response to dose adjustment).
b. Patients who become hypoxic (<90% O2 saturation on room air) or sedated (OASS scale score <4) will be referred/transported to the ED (call 911); CBD dose will be held until medical assessment and stabilization, and if restarting medication is deemed appropriate by the study MD, the daily total study medication dose will be halved.

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