Official Title:	A Phase I/II, Randomized, Double-blind, Placebo-controlled, Single-center Study of the Effects of Cannabidiol (CBD) on Opioid Plasma Levels in Participants With Chronic Radiculopathic Pain Syndromes Maintained on Chronic Opioid Therapy (COT)
NCT Number:	NCT04760613
Study Number:	21-00230
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Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
1.0	05/20/2021	Original Version
2.0	7/27/2021	1) Clarification about Certificate of Confidentiality from NIDA automatically generated (p. 13) 2) Storage of study drugs location clarification. Use of NYU-HHC CTSI investigational pharmacy (p. 29) 3) Correction of study drug dispensation/accountability log and study drug participant self-administration log (p 29) 4) Correction of visit T5 to T6 (p. 30) 5) Updated/Corrected Schedule of assessments (p. 31) 6) Clarification of SCID-5 version and use (p. 33) 7) Clinical Opioid Withdrawal Scale replaced with Subjective Opiate Withdrawal Scale for ease of administration (p. 34) 8) Baseline erroneously listed twice in QoL section (p. 35) 9) T4 visit corrected to include pharmacokinetic assessment (p. 38) 10) T9 visit corrected to include collection of urine for drug test and pregnancy test (p. 41) 11) Medical monitor now listed as PI Stephen Ross (p. 49) 12) Specification of DSMB members (p. 51) 13) Correction of participant reimbursement at T6 visit (p. 61) 14) Updated/Corrected Schedule of assessments (p. 74)
3.0	11/11/2021	1) Removal of John Rotrosen MD as co-I
4.0	11/16/2021	1) Addition of CBD trough levels (p. 15-16, 34, 37-39) 2) Corrections of time assessments for pharmacokinetic analysis (p. 3, 15-16, 35) 3) Correction to hyperlinks (p. 18, 42) 4) Correction of blood specimen storage temperature (p. 36) 5) Addition of Visit Number to blood specimen labels (p. 36) 6) Correction to blood specimen shipment frequency (p. 36) 7) Added name of specimen tracking log (p. 36) 8) Corrections to Schedule of Assessments (p. 31, 74) 9) Spelling, punctuation, and formatting corrections
5.0	1/6/2022	1) Fixed Table of Contents pages (p. iv-vii) 2) Added Epic/DataCore to Recruitment Strategies (p. 19) 3) Added Medication Self-Administration Log to Screening and Baseline Visits (p. 74) 4) Added COVID-19 as possible reason for participant termination/withdrawal (p. 20) 5) Added PI discretion for Field Sobriety Tests regarding disability (p. 43) 4) Spelling, punctuation, and formatting corrections
6.0	2/28/2022	1) Fixed year for last modification date 2) Changed “trough” language to “plasma” (p. 2, 14-16, 32, 34, 36-40, 53-54) 3) Specified opioid & CBD blood draw timing (p. 15-16, 36-37)

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Version Number	Version Date	Summary of Revisions Made
7.0	6/3/2022	**Primary Changes to Study Design** 1) Primary Efficacy Outcome now assessing pain (p. 1, 14-16, 31, 71) 2) Opioid sparing is now an exploratory outcome (p. 2, 14-16, 51) 3) Removed MEDD, Communication with Provider, and Motivation to Change Opioid Use from Inclusion Criteria (p. 16) 4) Reduced opioid maintenance dose from 3 months to 1 (p. 1, 16) 5) Reduced study duration from 6 months to 2 weeks (13 visits reduced to 8, no follow-up period) 6) Added one 5-hr PK assessment during T3 (p. 34, 37, 38) 7) 40 participants reduced to 20 participants (p. 1, 3, 15, 20, 52) 8) Compensation increased from $240 to $400 (~$18/hr) (p. 58) 9) Removed COMM, SOWS, Motivation to Change Opioid Use, & Quality of Life measures (p. 14-16, 31, 36, 38, 51, 52, 71) **Changes to Schedule of Assessments (p. 31, 71)** 1) Removed visits T5-T9 2) Removed COMM, SOWS, Motivation to Change Opioid Use, Quality of Life 3) Changed Primary Efficacy Outcome to Pain 4) Moved LFTs to 1-week & 2-week 5) Added Birth Control Documentation to 1-day & 1-week 6) Added MEDD to 1-day & 2-day 7) Added Opioid Craving VAS to 1-day, 2-day, 1-week 8) Added Pain & Mental Health measures to 1-day, 2-day, 1-week 9) Moved Blinding Integrity to 2-week 10) Added Compensation to 1-day, 2-day, 2-week **Other Revisions** 1) Fixed titles (p. iii, 1, 46) 2) Changed PI address to new location (p. iii, 4) 3) Fixed Table of Contents pages (p. v-vii) 4) Adjusted study length and assessment dates (p. 1, 2, 3, 11, 12, 14-16, 20, 28, 29, 33-39, 49-51, 58) 5) Capitalized and added hyperlink to email (p. 4) 6) Moved Secondary Analyses to Exploratory Analyses/Outcomes and reordered (p. 2, 14-17, 49-53) 7) Removed mediational analyses (p. 53) 8) Added Depression & Opioid Craving to Exploratory Analyses (p. 2, 14-16, 49-52) 9) Removed Opioid-Related ADRBs (p. 2, 14-16, 35, 49-52) 10) Removed Opiate Withdrawal (p. 15, 16, 34, 52) 11) Removed Opioid Tapering Strategy (p. 17) 12) Moved Opioid Outcomes after Mental Health (p. 34) 13) Removed ELISA assays from PK assessment (p. 34) 14) Removed Bellevue Lab area (p. 11, 29, 30, 39) 15) Specified pregnancy alternatives (p. 13) 16) Added details about recruitment through physicians (p. 19) 17) Added ResearchMatch to recruitment strategies (p. 20-21) 18) Fixed Anxiety, Depression, and Sleep scales (p. 16, 34) 19) Added provision of naloxone kit (p. 17) 20) Removed erroneous assessment of abuse potential for CBD (p. 51) 21) Added Birth Control to Medical Screening (p. 32) 22) Adjusted DSMP participant numbers (p. 51)

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Version Number	Version Date	Summary of Revisions Made
8.0	7/11/2022	NIDA/NIH-Requested Revisions to DSMP 1) Changed “proof-of-concept” to “exploratory” (p. 1, 15) 2) Changed pain from primary efficacy to secondary (p. 1, 3, 16, 33, 51-53, 73) 3) Add acceptable forms of birth control (p. 13) 4) Add sentence about COT-induced hyperalgesia to Description of Study (p. 15) and Pain assessment description (p. 16) 5) Add sentence specifying that Primary Outcome is safety and PK effects (p. 16) 6) Add “stable dose of” to opioid maintenance inclusion criteria 7) Change “serious” to “clinically significant” for exclusionary laboratory abnormalities (p. 17) 8) Add exclusion criteria for positive urine toxicology at screening (p. 17) 9) Add exclusion criteria for alcohol level greater than 0 at screening (p. 17) 10) Make suicidality exclusion more stringent: any history of attempts (p. 17) 11) Add alcohol testing to Screening (p. 33, 37, 73) 12) Make SAE reporting more stringent: all SAEs regardless of relationship to study participation (p. 46, 48) 13) Add DSMB reporting requirement for all SAEs within 72hrs (p. 46, 47) 14) Add description of anticipated AEs of concern to Study Halting Rules (p. 47) 15) Fix erroneous grant number (p. 47) 16) Prior NIDA/NIH approval for changes to DSMP changed to “all significant changes to the protocol must be approved by NIDA Program Officer prior to implementation” (p. 48, 49) 17) Added annual DSM report to “Responsibility for Data and Safety Monitoring” (p. 49) 18) Specify numerical value for Hypothesis 1b (p. 14, 51) Other Revisions 1) Fix Brief Summary to include placebo comparison again (p. 1) 2) Add Weill Medical College of Cornell University as a referral source (p. 18) 3) Removed erroneous word “below” (p. 34) 4) Added parenthetical explanations to Hypotheses 1a & 2 for consistency (p. 51) 5) Adjusted Schedule of Assessments to include breathalyzer (p. 33, 73) 6) Formatting and punctuation changes
9.0	9/30/2022	Clarification regarding pregnancy testing and birth control documentation (p. 13): 1) Specified that it is unnecessary for participants incapable of bearing or fathering a child 2) Adjusted inclusion criteria to reflect that it only applies to men capable of fathering a child (p. 17)
10.0	10/26/2022	1) Fixed error in compensation structure (swapped T2/T3) (p. 60)
11.0	11/22/22	1) Indicated when the 5hr blood draw would take place on the S.O.A. (p. 33) 2) Expanded Screening window to account for additional screening visits (p. 33) 3) Added bullet for scheduling additional Screening Visits (p. 38)
12.0	12/13/22	1) Swapped out DSMB Member (p. 51)

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A phase I/II, randomized, double-blind, placebo-controlled, single-center study of the effects of Cannabidiol (CBD) on opioid plasma levels in participants with chronic radiculopathic pain syndromes maintained on chronic opioid therapy (COT)

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Study Product:	Cannabidiol (CBD)
Study Product Provider:	ANANDA Scientific
ClinicalTrials.gov Number:	NCT04760613

Initial Version: May 20, 2021

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonization ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

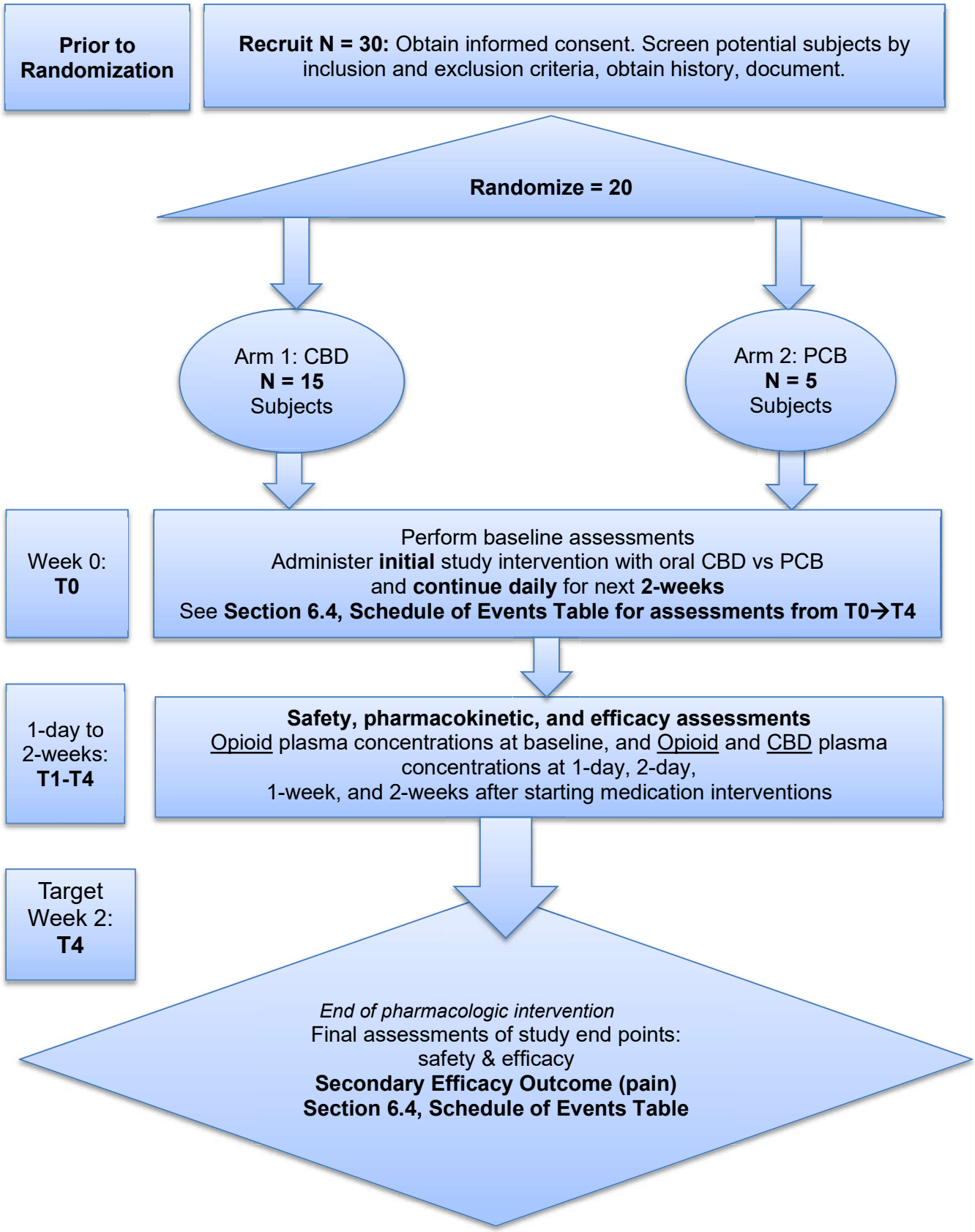
AE	Adverse Event/Adverse Experience
CBD	Cannabidiol
CNCP	Chronic Non-Cancer Pain
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
OUD	Opioid Use Disorder
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	A phase I/II, randomized, double-blind, placebo-controlled, single-center study of the effects of Cannabidiol (CBD) on opioid plasma levels in participants with chronic radiculopathic pain syndromes maintained on chronic opioid therapy (COT)
Short Title	CBD for chronic radiculopathy on chronic opioid therapy (COT)
Brief Summary	This double-blind, placebo-controlled, exploratory trial is designed to compare the effects of oral CBD 600mg to placebo (PCB) in 20 outpatients with chronic spinal radiculopathies (without co-occurring Opioid Use Disorder), maintained on stable opioid analgesics for a minimum of 1 month. The trial duration will be approximately 2 weeks (from the point of randomization) of daily CBD 600mg vs placebo. Safety and tolerability of CBD will be assessed throughout the trial. The secondary efficacy outcome is change in pain outcomes from baseline to end of the treatment period at 2-weeks post-randomization/initiation of treatment with a Mixed Model for Repeated Measures (MMRM) statistical analysis performed to assess between group treatment effects of CBD relative to placebo.
Phase	Clinical Study Phase I/II
Objectives	To collect preliminary safety, tolerability, and pharmacokinetic data for the use of CBD in patients with chronic non-cancer spinal radiculopathies maintained on COT. To obtain a preliminary assessment of efficacy of CBD in reducing pain catastrophizing.
Methodology	Randomized, double-blind, placebo-controlled, parallel design
Endpoint	AEs, plasma concentrations of opioids and CBD, and outcomes of pain, anxiety, depression, sleep, opioid craving, and opioid sparing.
Study Duration	2 years
Participant Duration	2 weeks
Duration of IP administration	2 weeks
Population	20 men and women (aged ≥18) with chronic spinal radiculopathies maintained on COT in the New York area
Study Sites	NYULH
Number of participants	30 participants expected to be enrolled; 20 participants to receive CBD or placebo over 2-week treatment period
Description of Study Agent/Procedure	Oral CBD 600mg administered daily over a 2-week treatment period
Reference Therapy	Inactive placebo
Key Procedures	Study questionnaires Blood draws EKG

Statistical Analysis	For Hypothesis 1a (safety and tolerability), the frequency of AEs will be analyzed and tabulated for each treatment group, and compared using chi-squared tests. The incidence of AEs will be summarized by system organ class, preferred term, the likelihood of its relationship to the treatment, and the severity for each treatment group. For Hypothesis 1b (plasma opioid concentrations), the respective outcomes will be analyzed with an MMRM to assess differences in change from baseline. The primary contrast is change from baseline to 1-day and 1-week post-randomization/initiation of pharmacologic treatment with secondary analyses contrasting changes from baseline to 2-weeks post-randomization. For Hypothesis 2 (pain), Hypothesis 3 (anxiety), Hypothesis 4 (depression), Hypothesis 5 (sleep), Hypothesis 6 (opioid craving), Hypothesis 7 (opioid sparing), the respective outcomes will be analyzed with *an MMRM* to assess differences in change from baseline. The primary contrast is change from baseline to end of the treatment period at 1-week post-randomization/initiation of treatment with secondary analyses contrasting changes from baseline to end of the treatment period at 2-weeks post-randomization.

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 *Background Information and Relevant Literature*

Need for novel, safe, non-addictive, non-opioid medications for patients with chronic non-cancer radiculopathy maintained on chronic opioid therapy (COT)

Chronic pain (pain lasting 3 or more months) (1) is a highly prevalent public health problem (2) (3), and constitutes the greatest economic burden of any medical condition (4). The most effective treatment strategy for chronic pain is an integrated approach of multimodal strategies across a variety of medical disciplines (i.e., pain medicine, anesthesia, physical medicine/rehabilitation, psychology/psychiatry) that incorporate a broad spectrum of treatments such as: physical therapy/rehabilitation, psychological (i.e., cognitive-behavioral therapy, mindfulness-based interventions), interventional (i.e., nerve blocks, neurostimulators, joint injections), pharmacologic (non-opioid and opioid), and other (i.e., acupuncture, massage, chiropractic) modalities (5, 6). However, such integrated/interdisciplinary pain treatment programs are rarely accessible (i.e., lack of insurance reimbursement, paucity of existing programs) to patients with chronic non-cancer pain (CNCP) and a vast number of efficacious non-opioid therapies are poorly reimbursed or unavailable in underserved and rural communities. By default COT was inappropriately prescribed as first line treatment (7). While there is an established evidence base to support the use of opioids for acute pain, cancer-related pain, and in end-of-life/palliative care (7), the data supporting COT for CNCP is very limited with few RCTs, limited sample sizes, and trial durations rarely over 3 months (1) (8-12). Further, only 30-50% of patients with CNCP respond to opioid analgesics (13) and the average reduction in pain in this population is only approximately 30% (14). Compounding this lack of evidence, there is abundant evidence of harms associated with COT in CNCP conditions including fractures, cardiac complications, immuno-suppression, endocrine abnormalities (i.e., opioid induced androgen deficiency), motor vehicle accidents, cognitive impairment, sleep disturbance, worsening of pain (due to opioid-induced hyperalgesia), opioid diversion, opioid abuse and development of opioid use disorders, opioid-induced respiratory suppression and overdose fatalities (8); and these adverse effects increase with dose and treatment duration (8), (15), (16). Estimates of the prevalence of opioid use disorders (OUDs) in CNCP range from 5% in a meta-analysis (17) to 20-35% (18), (19), (20), (21). All of this notwithstanding, COT prescribing for CNCP increased markedly between 1990 and 2010, and is one of the root causes of the current opioid epidemic (22).

Of the CNCP conditions, radicular pain disorders (particularly low back pain) have particularly high rates of opioid prescribing (23), and higher opioid doses predict poorer functional outcomes in this cohort of chronic pain patients (11). Radiculopathy describes a range of symptoms produced by compression of a nerve root in the spinal canal that can occur at varying areas along the spine (e.g., cervical, thoracic, lumbar). Radiculopathies are typically caused by changes in the tissues surrounding nerve roots including spinal vertebrae, tendons and intervertebral discs. Radicular pain can be caused by herniation of the nucleus pulposus (intervertebral disk), vertebral degenerative changes, bone spurs, and spinal stenosis. This leads to inflammation at the nerve roots and/or irritation of the dorsal root ganglion (24). Symptoms of radiculopathies frequently include: pain, numbness, weakness, and tingling (paresthesia). Lumbar radiculopathy occurs in the lower back, is the most common form of radiculopathy, and is often referred to as sciatica because the nerve roots of the sciatic nerve are often involved.

Our goal is to develop an intervention to reduce opioid use in patients with radicular CNCP syndromes receiving moderate to high-dose COT to safer doses while at the same time maintaining or improving pain management. We will exclude patients with co-occurring OUD. However, patients with chronic radiculopathies on moderate to high-dose COT are at elevated risk to misuse or abuse opioids, develop an OUD along a spectrum of aberrant drug-related behaviors (ADRBs) (i.e., use of opioid for reason other than pain, mood or anxiety management,

sleep induction, euphoria (15, 25), and to develop other complications from opioid use including overdose death. Although a variety of non-opioid pharmacologic treatments (i.e., NSAIDs, acetaminophen, anticonvulsants, anti-depressants, topicals, corticosteroids) are used to manage radicular CNCP conditions, their efficacy is limited, and none are known to be effective at both decreasing opioid use and pain in this patient population (26), (27). Further, although there are effective pharmacologic interventions to treat opioid withdrawal and achieve abstinence in patients with OUDs (28), there has been relatively little research on interventions to reduce COT in CNCP without co-occurring OUD, with only 5 RCTs [acupuncture, mindfulness, and CBT interventions (i.e., motivational interviewing)] in the published literature (29-33), and none of pharmacologic interventions. A meta-analysis of the 5 RCTs found mixed results for reductions in opioid use and pain and concluded that currently 'there is no evidence for the efficacy… of methods for reducing prescribed opioid use in chronic pain' (34).

Cannabidiol as a candidate drug for reducing the risk of developing an OUD in patients with radicular CNCP on COT: <u>Opioid Sparing</u>

Over the past decade, a rapidly growing body of pre-clinical research has suggested that Cannabidiol (CBD) is a highly promising candidate to treat substance use disorders (SUDs), including OUDs (35), (36), (37), (38), (39). In pre-clinical studies, high dose CBD decreases rewarding effects of morphine via actions at 5-HT1a receptors) (40). CBD alone may decrease opioid withdrawal in animals (41), although the data are inconsistent (42), and CBD may potentiate THC's effects in diminishing opioid-withdrawal (43), (44). Further, in an experimental rat model, CBD was associated with a reduction in cue-induced heroin seeking and reinstatement, with long-lasting effects over 2 weeks, associated with normalization of heroin-seeking-induced changes in GluR1-containing AMPA receptors and CB1 receptor expression in the nucleus accumbens (45). In rodents CBD mitigates heightened negative affect, impulsivity and disturbed reward behaviors associated with addiction (46).

In man, CBD may produce sustained anti-opioid craving effects. A small double-blind controlled trial in abstinent heroin dependent individuals showed 3 days of oral CBD (versus placebo) reduced cue-induced craving with effects lasting up to one week (47) (48). Further, a study in healthy subjects reported CBD did not potentiate subjective or physiological effects of fentanyl (49). Overall, animal and preliminary human studies suggest CBD has potential for preventing or treating OUDs by possibly reducing opioid reward and withdrawal, limiting reinstatement, mitigating behavioral imbalances known to perpetuate drug-seeking, and acting upon brain circuitry implicated in addiction with long lasting effects that suggest the potential for disease modification. It is possible that CBD could be used to prevent the progression to an OUD in patients with radicular CNCP on COT by affecting a reduction or elimination in dose of COT (i.e., decrease opioid withdrawal or craving). These promising anti-addictive effects of CBD may stem from its actions on the endocannabinoid system, which is recognized to play an important role in the pathophysiology and treatment of addiction (50). Although CBD has a low affinity for CB1 and CB2 receptors, it acts at these receptors respectively as an inverse agonist and as an antagonist (51); at the same time it indirectly facilitates endocannabinoid neurotransmission by inhibiting hydrolysis of the endocannabinoid anandamide by fatty acid amide hydrolase (FAAH) and reducing anandamide uptake by the anandamide membrane transporter (AMT) (52). In addition to its impact on the endocannabinoid system, CBD produces allosteric modulation of ligand-binding kinetics at μ and δ opioid receptors (53) and acts as an agonist at the serotonin 1A (5-HT1A) receptor (54).

CBD as a candidate drug for reducing chronic pain

Preclinical evidence supports the use of CBD as an anti-nociceptive treatment for radicular CNCP syndromes. In animal studies, CBD reduces pain behaviors and inflammation in chronic inflammatory pain models (55), (56), (57), (58) and displays anti-nociceptive effects in neuropathic pain models (56), (57), (59). Studies of CBD in humans for pain are limited.

Sativex®, an extract of cannabis consisting of equal parts of THC and CBD, has been studied in humans for neuropathic and cancer pain, with more promising results for neuropathic pain (60), (61), (62). In contrast, the effects of CBD alone on pain in humans are not well elucidated. A case series reported that daily oral CBD use (up to 150mg for 3 weeks) was well tolerated and reduced pain scores in seven kidney transplant patients with uncontrolled chronic pain (63). Another case series of oral CBD (up to 150mg/day over 3 months) in twelve females with pain associated with dysautonomic syndrome following HPV vaccination, reported that CBD was safely administered and associated with significant reductions in pain (64). CBD appears to mediate its anti-nociceptive effects by affecting multiple targets along descending inhibitory nociceptive pathways including vanilloid TRPV1 receptors (65), 5-HT_{1A} receptors (54), (66), glycine receptors (57), as well as indirect facilitation of endocannabinoid transmission via FAAH inhibition and AMT reuptake inhibition (52), (67).

Opioid sparing with CBD in patients with radicular CNCP on COT

In addition to the known anti-nociceptive effects of opioids and cannabinoids alone, the combination of opioids and cannabinoids can have synergistic effects in animal models of acute and chronic pain (68), (69), (70), (71), (72). In humans, additive or synergistic analgesic effects of opioids and cannabinoids have been observed in the electrical stimulation test (73) and for alleviating negative affect associated with thermal stimuli (74). Further, there is population-level evidence for a negative correlation between the availability of state medical marijuana programs and opioid use/overdose suggesting that patients with CNCP may be replacing opioids with cannabis for pain management (75), (76, 77); however, other data suggests that medical marijuana users may be more likely to report medical use of opioid analgesics in the past 12 months (78) and a recent study suggests that the association between medical cannabis laws and opioid overdose mortality has reversed over time (79). More research is necessary to determine the exact relationship between opioid and cannabinoid treatments in CNCP, but it is worth exploring if CBD could be used to decrease or eliminate the need for COT in patients with radicular CNCP (thereby reducing the risk of serious adverse events including overdose death and possibly preventing the transition to an OUD), while at the same time effectively managing pain.

Potential mediators of CBD effects on opioid use in radicular CNCP on COT: pain, anxiety, insomnia, depression, opioid withdrawal, opioid craving

Pain and OUD are intimately related. Opioids are often helpful for acute pain but their anti-nociceptive properties often diminish over time (or can worsen pain through opioid-induced hyperalgesia) and opioid-withdrawal can increase pain perception in a vicious cycle leading to increased opioid use and development of OUD (80). While opioids can acutely diminish anxiety, depression, and insomnia (which are very common conditions in patients with CNCP), opioid withdrawal worsens all of these symptoms and can trigger relapse in patients with a SUD (81). Also, anxiety and sleep disturbances typically worsen pain with sleep disturbances associated with reduced pain tolerance and leading to the release IL-6 pro-inflammatory cytokine (82). CBD may be effective in treating pain, anxiety, depression and insomnia in humans (83-85). So, in addition to CBD's potential direct effects of decreasing opioid use by blunting intoxication, craving, withdrawal, it may indirectly decrease opioid use or withdrawal symptoms by diminishing pain, anxiety, depression, and insomnia.

2.2 *Name and Description of the Investigational Agent*

CBD is a phytocannabinoid abundant in cannabis and has shown therapeutic effects across various medical, psychiatric, and addictive disorders (86). Unlike tetrahydrocannabinol (THC), CBD has no known addictive liability (87), lacks psychotogenic, intoxicating or rewarding effects, and has been safe and well-tolerated in humans up to high doses (88), (89). CBD possesses neuroprotective, anti-inflammatory, antioxidant, anticonvulsant, and analgesic properties (56),

(55). CBD is available as an FDA-approved medication (Epidiolex®) for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome (90). It is manufactured by GW Pharmaceuticals and is a schedule IV drug.

Existing data suggest CBD is safe to administer to humans. However, clinical data are limited, and its use in the treatment of patients with chronic radiculopathies maintained on COT is experimental. The data and safety monitoring plan in this trial is designed to ensure that the risks of medications and study-related procedures are minimized for patients. CBD remains a schedule 1 drug (even though CBD in the form of Epidiolex® is a schedule IV drug), a class defined as drugs with no known medicinal value and high potential for abuse. Despite this scheduling, CBD is not addictive (rather appears to have anti-addictive properties) and the recent 2018 Farm Bill in the US removed hemp from the controlled substances act (CSA) and therefore hemp-derived CBD is not a drug that falls under the CSA scheduling system. Even though CBD in the form of Epidiolex® is FDA-approved for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, its use for the treatment of chronic radiculopathies maintained on COT is experimental and therefore, this study will be performed under an Investigational New Drug Application (IND # 152957). Refer to ANANDA Scientific **Investigator's Brochure A1002N5S CBD in Liquid Nanodomains Oral Formulations** for comprehensive drug information.

2.2.1 Preclinical Data

See section 2.1 above.

2.2.2 Clinical Data to Date

See section 2.1 above.

2.2.3 Dose Rationale

There is no known data on optimal dosing of CBD in attempting to reduce maintenance opioid analgesic doses in CNCP, and oral CBD dosing is complicated by limited bioavailability, at approximately 6% (91). However, in a small pilot trial in abstinent heroin dependent participants that suggested sustained anti-craving effects of CBD, doses of 400mg and 800mg were safely administered (48). In a study in healthy participants, CBD (400mg and 800mg) was co-administered with intravenous fentanyl without reports of serious adverse events (49). Further, CBD has safely been administered to patients with chronic pain syndromes at oral dosing up to 150mg daily for up to 3 months (63), (64). Case reports suggesting anti-addictive effects of CBD in cannabis use disorder have used doses of CBD up to 600mg daily orally (39, 92), and in a study of the acute effects of co-administration of CBD and alcohol, CBD was administered at a dose of 200mg (93). Consistent anxiolytic effects of CBD have been observed with oral dosing in the range of 400-600 mg/day (94) and CBD has been safely given to patients with schizophrenia up to 1280 mg per day (95). In a currently approved NIAAA funded clinical trial at NYULMC (Effects of cannabidiol in alcohol use disorder; NCT 03252756), CBD will be administered to patients with alcohol use disorder at 600mg and 1200mg daily oral doses. In this trial of patients with CNCP on COT, we propose to use an oral daily dose of 600mg per day of CBD and to contrast the effects with placebo. Based on previous human studies, the proposed dose of 600 mg daily is expected to be well tolerated in humans and to yield steady state levels within a safe and potentially therapeutic range. CBD does not appear to be psychoactive in this dose range (94) and although it has historically been classified as a schedule I drug (recent FDA re-scheduling to IV for Epidiolex®), it has no known addictive liability (87), unlike THC (the main psychoactive and addictive component of the cannabis plant).

2.3 Rationale

There is growing evidence implicating the endogenous cannabinoid system in mediating neural processes involved in opioid use/addiction and pain. Preclinical and preliminary studies in humans suggest that cannabidiol (CBD) may be helpful in reducing opioid use and decreasing pain in patients with radicular CNCP syndromes, but no studies have yet been conducted of the effects of CBD in humans with radicular CNCP maintained on COT. This would be the first clinical trial exploring the effects of CBD in patients with radicular CNCP syndromes (without OUD but at risk for developing an OUD), maintained on COT, and to assess its safety and pharmacokinetics when co-administered with opioid analgesics and potential efficacy in reducing maintenance opioid dose, while potentially decreasing pain. This investigation is significant from a public health perspective because given the limited efficacy to high risk profile of COT in CNCP, there is an urgent need to develop novel, safe, and non-addictive, non-opioid pharmacotherapies that can both reduce the dose of maintenance prescription opioids and pain in patients with CNCP syndromes.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks & Risk Mitigation Strategies

2.4.1.1 Risks of experimental medication

Oral CBD has been administered in clinical trials to both healthy volunteers and patients with various medical conditions, as single or multiple doses ranging from 10 mg to 6000 mg (49, 89, 95-111). In most of the studies CBD was well tolerated and no severe or serious adverse events (AE) were reported. Hence, CBD is generally considered to have a favorable safety profile. It is noteworthy, however, that since clinical trials are conducted under widely varying conditions, the observed AE rates are difficult to compare and may not necessarily reflect those observed in practice. CBD safety has been further affirmed by the World Health Organization in a comprehensive monograph on this matter (112). Any adverse effects are therein considered more a result of drug-drug interactions between CBD and patients' existing medications than anything else. This premise is likewise stated in a review of CBD for treating epilepsy (90).

In a study published recently involving healthy volunteers, oral CBD doses of up to 6000 mg (single administration) and up to 1500 mg/d (multiple dose) were associated with only mild or moderate AEs, and none resulted in the early termination of participation (97). The most common AEs in all the trial arms were diarrhea, nausea, headache, and somnolence. Diarrhea and headache were more common in subjects taking CBD compared with placebo. The recommended dose of the FDA-approved Epidiolex® (mostly to children) ranges from 5 mg/kg/day to 5 mg/kg twice daily (10 mg/kg/day). Occasionally 20 mg/kg/day have also been administered. Since the drug has only been approved recently, no post-marketing safety data is available, and the following information is based on controlled and uncontrolled clinical trials experience. The most common adverse reactions that occurred in Epidiolex®-treated patients (incidence at least 10% and greater than placebo) were somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise and asthenia; rash; insomnia, sleep disorder poor quality sleep, and infections (113, 114). Overall transaminase elevations were observed in 14% of CBD-treated patients versus 3% in those receiving placebo.

In a human safety and PK study (see section *6.1 Study Agent(s) and Control Description Human safety and PK study with A1002 formulation*) conducted on the formulation of A1002N5S and a second, similar formulation, a total of 12 AE's occurred after the start of dosing. None were serious, all were considered mild, and none were considered related to the study drugs. The most frequent AE was headache (6/12, 50.0%) reported by 5 (out of the 15) subjects.

We do not anticipate any serious adverse events related to CBD administration in this trial. Subjects' participation in the trial will be subject to discontinuation in the event of serious medication side effects, or if continued participation was deemed unsafe by study personnel. Patients who are discontinued from the trial will have a final evaluation within one week, and will be given appropriate treatment referrals.

2.4.1.2 **Risks of potential drug-drug interactions: Metabolism, P450 system and opioids**

A detailed review on human metabolites of CBD—their formation, biological activity and relevance in therapy—has been recently published (115). CBD undergoes extensive hydroxylation by CYP450 mixed function oxidases at multiple sites, primarily the liver and gut. Seven recombinant human CYP enzymes were identified as capable of metabolizing CBD: CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 (116, 117). CYP2C19 is particularly dominant in formation of the active metabolite 7-hydroxy-cannabidiol (7-OHCBD) which is then further metabolized by CYP3A4 to its inactive metabolite 7-carboxy-cannabidiol (7-COOH-CBD). The enzymatic processes responsible for the formation of the metabolites also involve several UDP-glucuronosyltransferase (UGT) isoforms, including UGT1A9, UGT2B7 and UGT2B17 and sulfotransferases (91, 115-117). It should also be mentioned that inter-individual differences in the expression and function of CYP450 enzymes may considerably affect the pharmacokinetics of CBD and its metabolites, and this could be relevant in the therapeutic action and any possible adverse effects of CBD-containing preparations. There is limited evidence for effects of CYP450-metabolized drugs on the bioavailability or clearance of CBD except for CYP3A inhibitor ketoconazole and CYP3A inducer rifampicin. ketoconazole has been shown to double AUC of oral CBD and THC, while CYP3A inducer rifampicin reduced AUC by 2-fold (98). In the same study pretreatment with CYP2C19 inhibitor omeprazole did not affect CBD bioavailability, suggesting that bioavailability of CBD may not be compromised in patients with limited CYP2C19 metabolic capacity.

In summary, in vitro studies suggest that CBD is a potent inhibitor of CYP2C19 and CYP3A4 and a weaker CYP2D6 inhibitor (118-120). However, these in vitro studies found CBD IC_{50}s in the 2-10 μM range, which may equally well be described as "moderate" inhibition. Inhibitory constants (Ki)s were not calculated in these studies and so the observed values depended on the substrate concentration used to characterize the inhibition. In the Epidiolex registration trials CBD at doses ranging from 10-20 mg/kg/day were shown not affect the conversion of concomitantly administered clobazam to its active metabolite nor-clobazam (a CYP3A -mediated reaction) (121) but did affect clearance of nor-clobazam (a CYP2C19 mediated reaction). This result provides evidence that CBD is a significant inhibitor of CYP2C19, but does not support a substantial effect of CBD as an inhibitor of CYP3A at the 20mg/kg doses used. A case study of 13 y.o. girl demonstrated increased circulating methadone levels (CYP3A is central to methadone metabolism) (122), but the mother of the child had been administering 250mg of CBD 6 times a day for 14 days and the child had metastatic liver disease (123). No clinical evidence of CBD interaction with CYP2D6-metabolized drugs currently exists, but CBD has been shown to be a moderate-potent CYP2D6 inhibitor in vitro (120). Interactions with tacrolimus have been reported (124) although the patient was receiving 2000-2900 mg CBD/day. More information on interactions with many drugs commonly used for other indications is warranted when considering dose adjustment of either CBD or the concomitant medications. There are also potential concerns about interactions with drugs with a narrow therapeutic index with significant metabolism through the CYP2C9 isoenzyme family. In a case report of a 27 y.o. man on warfarin (significantly metabolized by CYP2C9) and smoking recreational cannabis (includes CBD and THC), there was a reported increase in International Normalized Ratio (INR) to 4.6 without any clinical sequelae (125).

There is no currently published data regarding the interaction between CBD and ethanol or grapefruit, although a study with ketoconazole, which like grapefruit juice can inhibit intestinal CYP3A4, induced a doubling of CBD bioavailability (98). In the same study CYP3A inducer rifampicin reduced CBD AUC by 2-fold and pretreatment with CYP2C19 inhibitor omeprazole did not affect CBD bioavailability.

Regarding potential drug-drug interactions with opioids and safety considerations, given that several prescription opioids are significantly metabolized by 2C19 (126, 127), it is theoretically possible that CBD could increase plasma and CNS concentrations of a participant's opioid medication if this drug is significantly metabolized by these CYP enzymes, and this could have important safety considerations such as opioid intoxication and overdose. We are aware of one trial where oral CBD (up to a dose of 800mg) was co-administered with an opioid (intravenous fentanyl) with no reports of serious adverse events; however, because plasma fentanyl concentrations were not detectable in this study, it is difficult to gauge the significance of the outcomes (48). By excluding participants taking opioids that are significantly metabolized by 2C19, we do not anticipate any significant or clinically relevant CBD-opioid interactions (i.e., signs of opioid intoxication, respiratory suppression, opioid overdose).

However, we will take extra precautions to mitigate the risk of CBD-opioid interactions that could potentially cause increased plasma and CNS opioid concentrations. Given that the terminal elimination half-life of oral CBD is approximately 24 hours (128), one can assume it would take approximately 1 week for the initial dosing of CBD to achieve a steady-state plasma level and that this would represent the period of greatest risk of opioid toxicity. Therefore, we will take the following extra precautions after initiating treatment with CBD:

- On the first day of CBD vs placebo administration (T1), and at 2-days (T2), 1-week (T3), and 2-week (T4) after initiating CBD vs placebo treatment, participants will be administered the first daily morning dose of medication (CBD 300mg- six 50mg capsules, or placebo) for that treatment period, after a light meal, and will be evaluated for at least 3 hours at a supervised clinical laboratory setting within the NYU-HHC Clinical & Translational Science Institute (NYU-HHC CTSI) at Bellevue Hospital before discharge home. After administration of study drug or placebo until discharge for all visits, participants will be continuously monitored by the study physician or CTSI nursing staff. Participants will be monitored with safety assessments with particular attention directed to detect any signs of opioid intoxication or overdose (i.e., physical examination signs, vital sign monitoring including respiration and oxygenation). Vital signs (blood pressure, pulse) will be obtained at a minimum of every 30 minutes by study staff or with increased frequency (including continuous monitoring) if clinically necessary. The use of continuous pulse oximetry monitoring will occur post administration of study drug or placebo until discharge from the clinic to assess oxygenation status. The study physician will assess for clinical signs and symptoms suggestive of opioid intoxication or overdose (i.e., miosis, respiratory suppression, decreased oxygenation, sedation/lethargy), and will take appropriate medical steps to assure patient safety (i.e., Narcan administration, oxygen administration, inpatient hospitalization, breaking the blind, discontinuing study medication). The Richmond Agitation-Sedation Scale (RASS) (*see section **7.1.1 Study Specific Procedures for details***) will be used to assess clinician-rated somnolence or sedation. Participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test (one-leg stand, finger-finger test, Romberg's test, walk-and-turn task, and counting backwards) (129). If there are no AEs during this time period or lasting intoxicating effects of the study drug (e.g., participants are able to pass field sobriety

tests several hours after study drug administration), participants will be dispensed the proper quantity of study drug (CBD or placebo) to self-administer daily at home until the next scheduled study visit.

- We will advise participants of possible CBD-opioid interactions, and ask them to report exacerbation or decrease of the effects of opioids during treatment, should this occur. This will be reported as routine outcome data, or in the case the interaction results in adverse symptoms, it will be reported as an adverse effect. We will closely monitor for subjective adverse effects throughout the study, especially for signs and symptoms that may indicate increased opioid concentrations. If necessary, at any point for safety reasons, we will break the blind if there is the possibility of serious adverse CBD-opioid interactions and take appropriate steps to assure safety of the participant. Participants will also be counseled about how to recognize adverse events, and will be provided with a contact number to reach study personnel in between these weekly interviews.

Regarding the potential effects of CBD on interactions with drugs with significant CYP 3A4 interactions, there are potential concerns of drug-drug interactions especially with CYP3A4 inhibitor ketoconazole and CYP3A4 inducer rifampicin. As such we will exclude medications primarily or significantly metabolized by CYP3A4 (i.e., ketoconazole, rifampicin) but will not exclude opioids (i.e., hydrocodone, oxycodone) that are partially metabolized through 3A4 (126). In addition, given that CBD is a weak inhibitor of CYP2D6, we will not exclude medications (including opioids) that are metabolized partially by 2D6 (i.e., hydrocodone, oxycodone) (126). We will exclude drugs with a narrow therapeutic window and significant metabolism through the CYP2C9 isoenzyme family with potential for clinically significant drug-drug interactions (i.e., warfarin). Given that grapefruit juice is a significant inhibitor of CYP 3A4, we will instruct participants to avoid consuming grapefruit or grapefruit juice during the duration of the study.

2.4.1.3 Risk of hepatocellular injury and adverse CBD-valproate interactions

CBD (in the form of Epidiolex™) has been reported to be associated with dose-related elevations in liver transaminases (ALT and/or AST). Increased levels of ALT were more pronounced than AST, suggesting that the liver was the source of this occurrence. There also was a clear dose association: 8% elevations overall in the 10 mg/kg group and 16% in the 20 mg/kg group (113, 114). Elevated liver enzymes do not necessarily signal a serious liver problem. There do not appear to be reports of CBD-treated patients who have experienced liver failure, and CBD may actually have therapeutic utility in treating liver conditions associated with alcohol, inflammation use, oxidative stress and steatosis (130). Identified risk factors for transaminase elevation included concomitant treatment with valproic acid (a medication used to treat seizure disorders, mood conditions and migraine headaches), elevated baseline liver function tests, and higher doses of cannabidiol. Most events of transaminase elevation occurred within 30 to 90 days after initiation of CBD treatment although rare cases were observed up to 200 days after initiation of treatment, particularly in patients also taking valproic acid. These abnormalities generally resolved with discontinuation of cannabidiol or dose decreases in cannabidiol or valproic acid, yet elevated levels also resolved spontaneously without changing the dose of CBD (113).

Given that CBD can cause dose-related elevations in liver transaminases, potential participants with elevated baseline transaminase levels ≥ 2 times the upper limit of normal (ULN) will be excluded from trial participation. Further, in addition to obtaining baseline liver function tests (LFTs), after initiating study medication or placebo, subsequent LFTs will be obtained at 1-week and 2-weeks (final study visit). If participants develop clinical signs and symptoms suggestive of significant hepatic injury (i.e., nausea, vomiting, right upper quadrant pain, anorexia, fatigue,

jaundice, dark urine), they will be immediately evaluated medically with an assessment of LFTs and appropriate medical steps will be taken to assure patient safety (i.e., breaking the blind, discontinuing study medication, hospitalization). Any subject who has LFTs ≥ 2 x ULN will be discontinued from study participation and will be referred for appropriate follow-up. Given the known adverse drug-drug interaction between CBD and valproate (in terms of hepatic function), we will exclude potential participants who are on valproate.

2.4.1.4 Risk in sexual reproduction

Risks of CBD in pregnancy, lactation, and sperm are unknown. Therefore, pregnancy and lactation are exclusion criteria, and participants capable of bearing or fathering a child will be required to document birth control use and be offered pregnancy testing throughout the study. All participants will be informed of the potential risks.

If the participant is biologically male, they will not be offered pregnancy testing. If they are capable of fathering a child, they must document birth control use throughout the study. If they are incapable of fathering a child (e.g., vasectomy), they will not need to document birth control use.

If the participant is biologically female or intersex and not of childbearing potential (e.g., bilateral oophorectomy, menopause with >1yr since last menstruation), they will not be offered pregnancy testing and will not need to document birth control use. If the participant is of childbearing potential, they will be required to document birth control use and will be offered pregnancy testing throughout the study, even if their sexual preferences and/or behaviors will not lead to pregnancy.

If the participant is pregnant, they will be asked to discontinue participation in this study and will be referred to their primary care physician. If a participant becomes pregnant while in this study, they will immediately contact their study physician and will be counseled as to possible alternatives to study participation.

Any participant capable of bearing or fathering a child must be willing to practice appropriate and reliable birth control. Acceptable forms of birth control for all trial participants are as follows:

- Hormonal methods like birth control capsules, patches, vaginal rings, or implants
- Barrier methods such as condoms or a diaphragm used with spermicide (i.e., foam, cream or gel that kills sperm)
- Intrauterine device (IUD)
- Vasectomy
- Sexual abstinence (from intercourse from which pregnancy may occur)
- Monogamous relationship with a vasectomized partner
- Monogamous relationship with a partner of non-childbearing potential
- Same-sex relationship

2.4.1.5 Risks to confidentiality and privacy

There is a risk for the identity of a participant to be disclosed to non-study personnel, resulting in a loss of privacy and a potential risk to reputation. This risk is estimated to be extremely low due to the various protections listed below, which include obtaining a certificate of confidentiality. In addition, information from this study may be submitted to the U.S. Food and Drug Administration (FDA) and NIH/NIDA. Records which identify subjects and the consent form signed by subjects may be inspected by the FDA, NIH/NIDA, and the NYU Medical Center Institutional Review Board. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this research project may be presented at meetings or in publications. However, the identity of individual subjects will not be disclosed in those presentations. In this

study participants will be asked about drug use and other possibly illegal activities. The researchers will keep information as confidential as possible, but complete confidentiality cannot be guaranteed. On rare occasions, research records may be subpoenaed by a court. Exceptions to the protection of a participant's confidentiality would occur if it were learned that the participant was a danger to him/herself or to others, that a child had been abused or neglected, or that an elder or dependent had been abused. Should this happen, the appropriate authorities would be notified, as required by law.

Confidentiality of research material will be ensured by storing the research materials in locked cabinets. Permission for access must be granted by the PI. Material will be available only to project staff, and only as needed. All project staff will be thoroughly trained in issues relating to confidentiality. Participants will be identified in case report forms (CRFs) by initials and an identification code. Data will be entered into TrialMaster®, a 21 CFR 11 compliant system at NYULH, a program designed specifically to protect patient privacy and confidentiality. Published reports will be based on group data; no individual data will be reported. As a further protection to confidentiality, and because this trial is funded by NIH/NIDA, a certificate of confidentiality has been automatically generated by NIH/NIDA (https://grants.nih.gov/policy/humansubjects/coc/how-to-apply.htm). With this Certificate, the investigators cannot be forced (for example by court order or subpoena) to disclose research information that may identify individual patients in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of NIH/NIDA for audit or program evaluation purposes. NIH/NIDA ensures confidentiality of requested data. Participants will be notified in the informed consent that the Certificate of Confidentiality does not prevent them or a member of their family from voluntarily releasing information about themselves and their involvement in the research. If an insurer, employer or other person obtains their written consent to receive research information, then the researcher may not use the Certificate to withhold that information. Participants will also be informed that the Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without their consent, information that would identify them as a participant of the research project under the following circumstances: the present danger of child abuse, suicide, and/or homicide.

2.4.1.6 Risks of blood draws

For most people, needle punctures for blood draws do not cause any serious problems. However, they may cause bleeding, bruising, discomfort, infections and/or pain at the needle site, or dizziness.

2.4.1.7 Risks of assessment procedures

There are no known psychological risks associated with the questionnaires used in the study, all of which have been used extensively in clinical populations. It is possible that discussion of substance use and psychiatric symptoms may cause emotional discomfort in some participants. One of the investigators of the project will be available to meet with any participant who becomes distressed about any aspect of the protocol and wishes to discuss this. Further, with respect to minimizing the discomfort that may result from the interview, research coordinators or research data associates are selected based on their personal attributes and interpersonal skills as well as their substantive knowledge. They are further trained and periodically observed to ensure that they are respectful and sensitive to the needs and feelings of the subjects in all contacts. Furthermore, they are trained to recognize signs of significant stress or enervation and are instructed that they should gently terminate the interview, perhaps to re-approach the subject at another time, whenever distress is observed.

2.4.2 Known Potential Benefits

Subjects may or may not experience clinical benefit from this study. Pre-clinical and clinical data suggest a possibility that the study drug (CBD) could produce anxiolytic, anti-addictive, and anti-pain effects. Components of study participation that are likely to be of benefit to participants include free psychiatric and medical evaluations, and the support and attention of participating in a clinical trial.

Objectives and Purpose

3.1 *Primary Objective*

Aim 1 (Safety): To collect preliminary safety, tolerability, and pharmacokinetic data for the use of CBD in patients with radicular CNCP syndromes maintained on COT. Hypothesis 1a: Compared to placebo, CBD will be well tolerated by participants with no treatment-related serious adverse events (SAEs) or persisting CBD-related AEs. Hypothesis 1b (plasma opioid concentrations): Compared to placebo, CBD will not increase plasma opioid concentrations (relative to baseline) by greater than or equal to 150% at any of the assessment time-points post-randomization (1-day, 2-day, 1-week, and 2-weeks).

3.2 *Secondary Objective*

Aim 2 (Efficacy): To obtain a preliminary assessment of efficacy of CBD vs placebo in reducing pain. ***Secondary Outcome (Pain)***: Hypothesis 2: Relative to baseline, CBD will be associated with a greater reduction in pain measures (pain catastrophizing and pain intensity/pain-related interference) compared to placebo at **week 2**.

3.3 *Exploratory Objectives/Aims*

3.3.1 Exploratory Objectives. The objective is to obtain a preliminary assessment of efficacy of CBD vs placebo in reducing anxiety, depression, insomnia, opioid craving, and opioid use.
Exploratory Aim 1: Compared to placebo, CBD will be associated with a greater reduction in anxiety relative to baseline.
Exploratory Aim 2: Compared to placebo, CBD will be associated with a greater reduction in depression relative to baseline.
Exploratory Aim 3: Compared to placebo, CBD will be associated with a greater reduction in insomnia relative to baseline.
Exploratory Aim 4: Compared to placebo, CBD will be associated with a greater reduction in opioid craving relative to baseline.
Exploratory Aim 5: Compared to placebo, CBD will be associated with a greater reduction in opioid use relative to baseline.

Results will serve as proof of concept, inform us about the safety and potential efficacy of this approach, and guide the design of a larger clinical trial.

4 Study Design and Endpoints

4.1 *Description of Study Design*

The proposed study is a phase I/II, double-blind, randomized, exploratory study designed to assess feasibility, safety, pharmacokinetics, and to contrast effects of CBD treatment to those of placebo on pain outcomes in patients with chronic non-cancer spinal radicular pain syndromes maintained on COT. We will specifically evaluate the safety of a 2-week, daily CBD treatment regimen in a chronic pain (radiculopathies) population maintained on COT, assess the impact of CBD on pharmacologic and psychological domains in patients with chronic radiculopathies maintained on COT, and to generate preliminary data on the impact of CBD on pain catastrophizing and interference, anxiety, depression, sleep quality, opioid craving, and opioid

sparing in this patient population. Many patients with chronic radicular pain syndromes who are maintained on COT may have COT-induced hyperalgesia, and it is possible, therefore, that a reduction of COT dose might produce a reduction in chronic pain. Following screening and baseline assessments, 20 participants will be randomized in a 3:1 ratio to receive either 600mg CBD/day (PO) or placebo for 2 weeks. Safety and tolerability of CBD will be assessed throughout the trial. Opioid analgesic maintenance dose will be assessed at baseline and longitudinally. Opioid analgesic plasma concentrations will be collected at the same time relative to when participants take their daily opioid analgesic medications at baseline (prior to initiating pharmacologic treatment) and all subsequent visits: 1-day, 2-day, 1-week, and 2-weeks. CBD plasma concentrations will be obtained at study visits following initiation of study drug administration (1-day, 2-day, 1-week, and 2-weeks) and will occur at the following time assessment points at these visits: trough (pre-dose), 1-hour post drug administration, and 3-hours post drug administration, with an additional sample collected 5-hours post drug administration at T3 visit (1-week).

4.2 *Study Endpoints*

4.2.1 Primary Study Endpoints

Primary Outcome

Establishment of the safety and pharmacokinetic effects of 300mg CBD BID on plasma levels of the following opioid analgesics in pain patients on a daily regimen: morphine, hydrocodone, oxycodone.

Safety

Safety will be assessed by collection of adverse events at all visits after treatment is initiated. Liver function tests (LFTs) will be obtained at screening, 1-week, and 2-weeks after initiating study medication or placebo to assess liver function during treatment with study medication. Any subject who has LFTs ≥ 2 x ULN will be discontinued from study participation and will be referred for appropriate follow-up. Risk of suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (131). Extensive safety monitoring (see ***Safety Oversight*** section below for details) will occur at the CTSI for all study visits, to assess for any clinical signs of opioid intoxication/overdose.

Pharmacokinetics: Plasma Opioid and CBD concentrations

Opioid analgesic plasma concentrations will be collected at the same time relative to when participants take their daily opioid analgesic medications at baseline (prior to initiating pharmacologic treatment) and at all subsequent visits: 1-day, 2-day, 1-week, and 2-weeks. CBD plasma concentrations will be obtained at study visits (1-day, 2-day, 1-week, and 2-weeks) following initiation of study drug administration. Samples will be collected at the following time assessment points at these visits: trough (pre-dose), 1-hour post drug-administration, and 3-hours post drug administration, with an additional sample taken 5-hours post drug-administration during the T3 visit.

Primary efficacy endpoint: None

4.2.2 Secondary Study Endpoints: Effects of CBD vs placebo on pain outcomes:

Pain: Participants in this trial with chronic radicular pain syndromes who are maintained on COT may have COT-induced hyperalgesia, and therefore, we expect a reduction of COT dose might produce a reduction in chronic pain. Pain will be assessed by measuring pain catastrophizing [with the Pain Catastrophizing scale (PCS)] (132) and pain intensity/pain-related interference [with the Brief Pain Inventory (BPI)] (133) assessed at baseline, 1-day, 2-day, 1-week, and 2-

weeks. The secondary efficacy outcome will be assessment of change in pain from the baseline visit to 2-weeks post-initiation of treatment.

4.2.3 Exploratory Endpoints

Anxiety: Anxiety will be assessed with the PROMIS® (134) (Patient-Reported Outcomes Measurement Information System) anxiety scale (long form) assessed at baseline and the following post-randomization time-points: 1-day, 2-day, 1-week, and 2-weeks.

Depression: Anxiety will be assessed with the PROMIS® (134) (Patient-Reported Outcomes Measurement Information System) depression scale (short form) assessed at baseline and the following time-points: 1-day, scale (135), at baseline and the following time-points: 1-day, 2-day, 1-week, and 2-weeks.

Opioid Craving will be measured with the Visual Analog Scale (VAS) (136) assessed at baseline and the following time-points: 1-day, 2-day, 1-week, and 2-weeks.

Sleep disturbances will be measured with the PROMIS® Sleep-Related Impairment (SRI) short form (135), at baseline and the following post-randomization time-points: 1-day, 2-day, 1-week, and 2-weeks.

Opioid maintenance dose will be measured in morphine equivalent daily doses (MEDD) assessed at screening, baseline, 1-day, 1-week, and 2-weeks.

5 Study Enrollment and Withdrawal

5.1 *Inclusion Criteria*

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Males and females aged ≥18
- Diagnosis of radicular CNCP (i.e., lumbar, cervical, thoracic)
- Maintained on stable dose of opioid therapy for a minimum of 1 month
    - Note: Only opioid pharmacotherapies using immediate or sustained release versions of morphine, hydrocodone, oxycodone will be allowed
- Able to provide voluntary informed consent
- If a person of reproductive potential, are willing to use approved form of contraception from screening for duration of the trial

5.2 *Exclusion Criteria*

An individual who meets any of the following criteria will be excluded from participation in this trial:

- Exclusionary medical conditions (e.g., unstable cardiac, hepatic, renal, neurologic illness) or any medical illness that in the opinion of the study physician poses a potential medical danger to the participant
- Exclusionary laboratory abnormalities (clinically significant abnormalities of complete blood count or chemistries, significantly impaired liver function[2])
- Current substance use disorder (including Opioid Use Disorder) other than nicotine or caffeine
- At screening, a positive urine toxicology test for: amphetamines (AMP), barbiturates (BAR), buprenorphine (BUP), benzodiazepines (BZO), cocaine (COC), 3,4-

methylenedioxymethamphetamine (MDMA), methamphetamine (MET), methadone (MTD), phencyclidine (PCP), and tetrahydrocannabinol (THC)
- At screening, an alcohol level greater than 0 on a breathalyzer
- Severe psychiatric conditions including past or current DSM5 diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder
- Current significant suicidality (assessed using the C-SSRS), any suicidal behavior in the past 12 months, or any history of suicide attempts
- Current use of recreational or medical cannabis or any product containing CBD
- Pregnancy or lactation
- Current use of concomitant medications metabolized primarily by CYP2C19 isoenzymes
- Current use of concomitant medications significantly or primarily metabolized by CYP3A4 with the potential for adverse drug-drug interactions with CBD (i.e., ketoconazole, rifampicin)
    - Note: Participants will be instructed to avoid grapefruit juice during the duration of the study
- Current use of concomitant medications with a narrow therapeutic window significantly or primarily metabolized by CYP2C9 with the potential for adverse drug-drug interactions with CBD (i.e., warfarin)
- Current use of concomitant medications known to have adverse drug-drug interactions with CBD (i.e., valproate) or the potential to cause significant drug-drug interactions (i.e., clobazam).
- Known allergy to CBD or any ingredient of the study compound
- Currently enrolled in a clinical trial assessing the effects of an anti-pain intervention

[1]Per the July 2020 FDA drug safety communication (https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-health-care-professionals-discuss-naloxone-all-patients-when-prescribing-opioid-pain), the study team will communicate with all clinicians prescribing opioids to subjects enrolled in study that they provide a naloxone prescription for each participant. If a participant does not have access to naloxone, study staff will provide them with a naloxone kit.

[2]Significantly impaired liver function is defined as: Liver Function Tests (LFTs) ≥ 2 x upper limit of normal (ULN).

5.3 *Vulnerable Subjects*
No vulnerable populations will be included in this clinical trial.

5.4 *Strategies for Recruitment and Retention*
Drs. Doan (co-I) and Wang, anesthesiologists with expertise in pain and with access to patients with radiculopathic CNCP on COT in the NYULH system, and Dr. Ross will initiate contact with potential participants through a multimodal approach including contacts with treating clinicians in pain clinics throughout the NYULH but in particular at the following clinics where Drs. Doan and Wang treat patients with CNCP syndromes:

Center for the Study and Treatment of Pain
Department of Anesthesiology, Perioperative Care and Pain Medicine
240 E 38th St, 14th floor
NY, NY 10016
Yearly total visits: 3416
New patients per year: 1766

Center for the Study and Treatment of Pain – Preston Robert Tisch Center for Men's Health

Department of Anesthesiology, Perioperative Care and Pain Medicine
555 Madison Ave
NY, NY 10022
Yearly total visits: 666

Center for the Study and Treatment of Pain – NYU Langone Seaport Orthopedics
Department of Anesthesiology, Perioperative Care and Pain Medicine
233 Broadway, Suite 640
NY, NY 10279
Yearly total visits: 1100

Other potential sites for recruitment within the NYULMC system will include patients at pain clinics at: Bellevue Hospital, the Manhattan VA, and Lutheran Hospital. Active recruitment will also take place through direct advertising (i.e., newspaper, radio) and social media sources (i.e., Facebook, Twitter). Note that the recruitment materials will be submitted via modification following initial IRB approval and prior to use.

To optimize recruitment, we have a large number of potentially eligible patients across recruitment sites at NYULMC and in the local NYC area, and recruitment will be led by co-investigators in the NYULMC Anesthesia Department (Dr. Wang, Dr. Doan), who are experts in pain medicine and have access to patients within the NYULMC system with radicular CNCP syndromes. If recruitment within the NYULMC system does not yield enough participants, we will reach out to other institutions with treating clinicians in pain clinics throughout the Metropolitan area (e.g., Weill Medical College of Cornell University).

If recruitment lags, strategies would include examining recruitment strategies and modifying or increasing them as necessary. Regarding retention, we will include procedures to optimize retention rates including weekly reimbursements, medical management, and tracking forms. If follow-up rates fall below 85%, we will re-evaluate and optimize these procedures accordingly. If this is a frequent occurrence, we would examine screening procedures, increase contact with participants, and consider altering the reimbursement schedule to enhance retention.

5.4.1 *Collaboration with Treating Physicians [TPs] for Recruitment Purposes*

This study will utilize a multimodal approach for recruitment, including collaboration with treating clinicians in pain clinics throughout the NYULH system and/or Metropolitan area. A member of the study team will initiate contact with potential participants through the following methods:

- Treating physicians will independently discuss the study with potentially eligible participants
    - If the patient is interested, the TP will contact a study team member with the patient's contact information or MRN (to obtain contact information)
    - Study team member will contact the patient to request a pre-screening telephone interview to determine eligibility for a screening visit
- Treating physicians will discuss the study with potentially eligible participants with help from the study team
    - Physicians will provide their schedule to the study team through EPIC
    - Study team will review the TP's upcoming patient visits and provide them with a list of potentially eligible patients
    - TP will discuss the study with potentially eligible patients or study team will obtain the TP's permission to directly contact potentially eligible patients on behalf of TP by [letter, phone, MyChart, email, and/or going to the facilities] to ask if they're interested in participating. These recruitment materials are uploaded in RNAV.
- Any recruitment information (as well as any contact with potential or enrolled participants) sent by email will utilize [Send Safe] email methodology.

- Should the potential participants agree, the study team will provide the participants with information regarding the next steps for study participation.

5.4.2 *Use of DataCore/EPIC/ResearchMatch Information for Recruitment Purposes*

This study will utilize DataCore/EPIC and ResearchMatch to identify potentially eligible study participants. The following process will be utilized regarding the use of EPIC/ResearchMatch for recruitment:

- The data will be gathered by requesting a report of potentially eligible participants through DataCore or ResearchMatch
- The data will be used for several purposes including:
    - Identifying potentially eligible participants who may meet core study entry criteria such as diagnosis of chronic radicular pain syndromes (i.e., cervical/thoracic/lumbar radiculopathy) and currently on opioid pharmacotherapies (i.e., morphine, oxycodone, or hydrocodone derivatives)
    - Contacting participants who are potentially eligible based on the DataCore/ResearchMatch queries to request a pre-screening telephone interview to determine eligibility for a screening visit
- The following study team members will have access to the EPIC/ResearchMatch search results:
    - PI
    - Research Coordinator
    - Research Project Manager
    - Research Data Associate
    - Co-investigators (i.e., involved in the recruitment process)
- The following data points will be used for the DataCore/ResearchMatch search:
    - Age ≥18
    - Diagnosis of chronic radicular pain syndromes (i.e., lumbar, cervical, thoracic)
    - List of current medications, including currently on an opioid pharmacotherapy allowed as part of study participation (i.e., morphine, oxycodone, or hydrocodone derivatives) or exclusionary medications (i.e., ketoconazole, rifampicin, warfarin, valproate, clobazam)
    - List of current known allergies
- Data will be discarded immediately after the recruitment targets have been met
- The study team will search EPIC every 2 months throughout the study until recruitment targets have been met
- After eligible, potential participants have been identified, their treating physicians (TPs) will be notified of this.
- The study team will obtain the TP's permission to directly contact potential participants on behalf of TP by [letter, phone, MyChart, and/or email] to ask if they're interested in participating. These recruitment materials are uploaded in RNAV.
- Any recruitment information (as well as any contact with potential or enrolled participants) sent by email will utilize [Send Safe] email methodology.
- Should the potential participants agree, the study team will provide the participants with information regarding the next steps for study participation.
- If a potential participant requests information regarding opting out of further recruitment for all research, they will be directed to contact the study coordinator or have them contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.5 Duration of Study Participation

The total duration of participant involvement, including screening and treatment visits, will be approximately 6 weeks. The total approximate time of contact during these 6 weeks is estimated at 24 hrs.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 30 participants are enrolled. It is expected that approximately 30 participants will be enrolled in order to produce 20 participants that can be evaluated to adequately assess study endpoints.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant fails to adhere to protocol requirements
- COVID-19 status significantly interferes with continued participation in the study

5.7.2 Handling of Participant Withdrawals or Termination

Every effort will be made to undertake the protocol-specified safety follow-up procedures to capture AEs, SAEs, and Unanticipated Problems. The investigator will attempt to obtain at a minimum survival data on all participants lost to follow-up. If a participant is lost to follow-up, they study team will attempt to contact the participant 3 times by telephone and twice by email. If the participant fails to respond, locators identified by the participant at screening will be contacted in the method specified by the participant. If participants withdraw, are terminated, or are lost to follow-up prior to the end of the 2-week treatment phase (prior to T4), they will be replaced to allow for 20 participants to complete the 2-week treatment phase (through T4).

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. Ross, NIH/NIDA, or the FDA. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

Nomenclature

Chemical name: Cannabidiol
IUPAC name: 2-(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl-5-pentylbenzene-1,3-diol

Structure

The chemical structure of CBD is shown below:

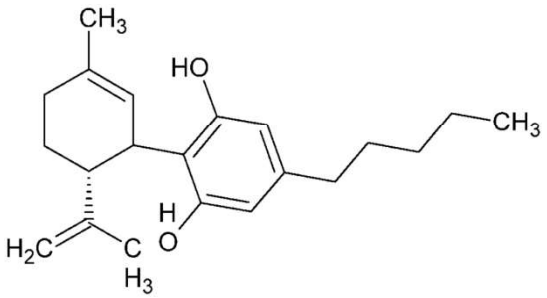


Figure 1 Chemical structure of C

Molecular formula: $C_{21}H_{30}O_2$
Molecular weight: 314.469 g/mol

The active ingredient in the Ananda investigational new drug (**A1002N5S**) is cannabidiol (CBD), extracted from hemp, at a 5% strength, produced and purified by Mile High Labs International (Colorado, USA). It is a white, crystalline powder free of particulates with a CBD potency of ≥98%.

Description of Liquid Nanodomains Oral Formulations

The novel formulation is based on the principle that a water-free mixture of some concentrated inactive ingredients (excipients) self-assemble spontaneously into liquid nanodomains that contain the active component CBD. CBD in such nanodomains is fully water soluble. In contrast, CBD alone is insoluble. Since the nanodomains are very small (10- 50 nm diameter) and thus have a very high surface-area-to-volume ratio, they have a high loading capacity of CBD at their interface.

Ananda Scientific Inc., in conjunction with LDS Technologies (Jerusalem, Israel), is currently developing a new, pharmaceutical-grade, highly pure form of CBD, extracted from hemp with improved bioavailability which is eventually intended for marketing approval by regulatory authorities in the United States and elsewhere as a pharmaceutical drug.

In a single-dose (50mg oral CBD), three-way pilot cross-over study in heathy normal volunteers, the A1002N5S formulation was shown to reduce T_{max} from about 2 hours to 1 hour (see clinical information section below) and increase absorption by about 40% over a CBD in oil reference compound.

Pre-clinical Information

Pharmacokinetics

The oral bioavailability of CBD is apparently very low, in some reports less than 10%. Absorption is slow and erratic, resulting in maximal plasma concentrations usually after more than 1 hour,

increasing with food and various lipid formulations. CBD is readily distributed throughout the body including brain tissue (i.e., crosses the blood-brain barrier). Plasma and brain concentrations are dose-dependent in animals. Like delta-9-tetrahydrocannabinol (THC), CBD may preferentially accumulate in adipose tissues due to its high lipophilicity. There are data showing that CBD undergoes extensive first pass metabolism. The resulting metabolites, most of which are physiologically inactive, are excreted in feces and urine. Based on animal and human studies, elimination of CBD from plasma is usually bi-phasic with an initial half-life ranging from approximately 1 to 3 hours and the terminal elimination half-life is in the order of 24 hours or longer (97, 113, 137).

Toxicology

The pre-clinical toxicology information presented in this section is derived from the Epidiolex® (an FDA-approved version of CBD for the treatment of Dravet's and Lennox Gestaut syndrome) non-clinical reviews, submitted by GW Pharmaceuticals to the FDA in October 2017 and approved in June 2018 (114). In a 26-week (gavage) Wistar rat study, no dose-limiting toxicity was observed. Slight (1.2-1.4-fold) increases in alanine transaminase (ALT) and alkaline phosphatase (ALP) were observed at the 50 mg/kg QD mid-dose (MD) and 150 mg/kg QD high-dose (HD). No effects were observed on sperm parameters; interstitial cell hyperplasia in ovary was observed at the MD and HD. In a 39-week Beagle dog study there were no deaths and the only clinical ramification was soft/liquid/mucoid feces. Decreases in absolute body weight (compared to control) were observed in all dogs. As in rats, the primary target organ was liver, with hepatocellular hypertrophy detected at all doses including 10 mg/kg low-dose (LD), accompanied by increases in ALT (slight) and ALP (up to 8-fold). A full battery of oral reproductive and developmental studies was conducted using purified CBD. Fertility and early embryonic development, embryo-fetal development (EFD), and pre- and postnatal development studies in Wistar rats were conducted using dose of 0, 75, 150, and 250 mg/kg. Toxicity expected at a high dose in these studies was not observed in females. In an EFD study in New Zealand White rabbit (0, 50, 80, and 125 mg/kg), adverse fetal effects (reduced body weight and increased variations) were observed at the HD, associated with maternal toxicity (body weight loss). There was no evidence of mutagenicity in a standard battery of genetic toxicology studies. The carcinogenic potential of CBD was assessed in a dietary carcinogenicity study in mice. No drug-related neoplastic findings were reported in two 13-week dose-ranging studies.

Pharmacokinetics of the Ananda Formulations in Rat

The PK profile of the Ananda formulations in rat was studied at Science in Action Ltd., (Israel). Blood samples were assayed for CBD concentrations at Analyst Research Laboratories (Israel) and the PK parameters were calculated from the data.

Sprague Dawley male rats (average weight 250g) received a single dose of 8 mg/kg (i.e., an average of 2.0 mg/animal) via gavage feeding. The CBD concentration in all formulations was 4.0 mg/mL. Blood samples for CBD plasma concentrations were collected at 0.25, 0.5, 2.0, 4.0, 8.0 and 12 hrs after dosing. 6 different formulations were evaluated and compared to a Control formulation (CBD in olive oil) at the same concentration. There were 5 animals in each group. Of the 6 formulations 2 were selected, due to their unique PK parameters, as candidates for a preliminary human PK study: A1002

Figure 1 displays the time-concentration curves of two selected formulations, compared to the Control, CBD in olive oil, preparation. **Table 1** outlines the average concentrations and the ratio between the new formulation and the Control formulation at each time point.

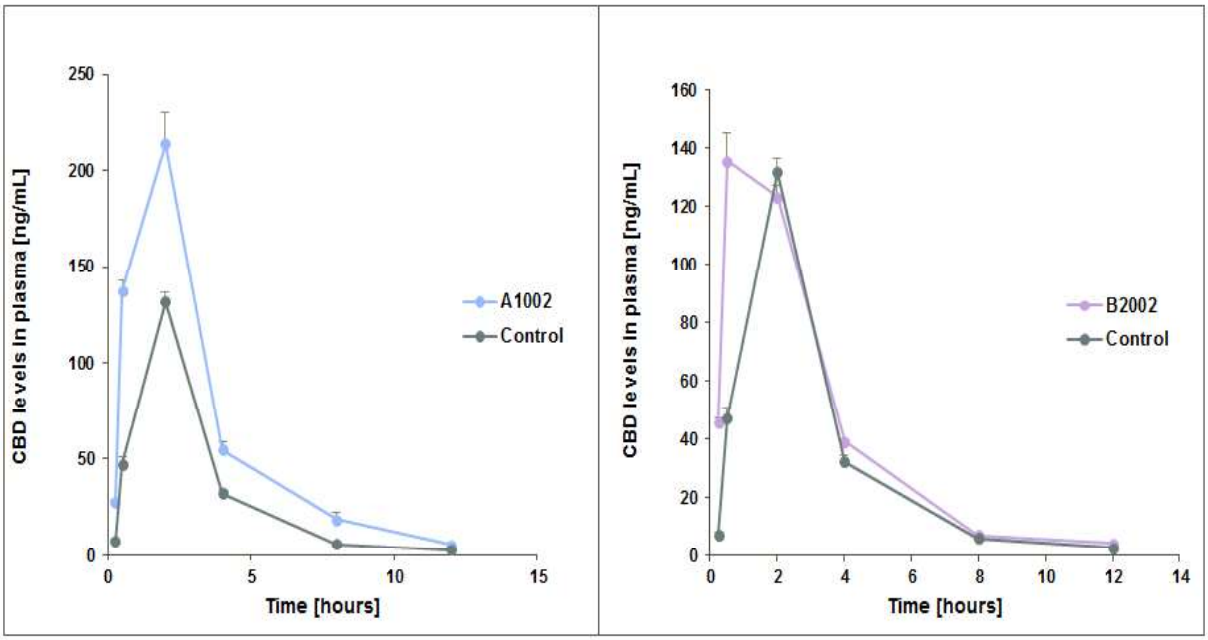


Figure 1 CBD Plasma concentration-over-time Curves

Table 1 Average CBD Plasma Concentrations per Time Point and IP/Control Ratio

Formulation	Time (Hr)	0.25	0.5	2.0	4.0	8.0	12.0
A1002 (N=5)	Ave (ng/mL) [SD]*	28.10 [0.76]	137.34 [5.49]	213.77 [16.82]	54.65 [4.42]	18.66 [3.58)	5.40 [0.58]
	Ratio**	3.86	2.90	1.62	1.69	3.13	2.08
Control	Ave (ng/mL [SD]*	7.28 [0.83]	47.43 [3.40]	131.68 [4.76]	32.29 [1.90]	5.97 [0.91]	2.60 [0.09]

*Ave: average, [SD]: Standard deviation
**Ratio: IP/Control

The PK parameters (T_{max}, C_{max} and AUC_{0-12}) are displayed in **Figure 2** and summarized in **Table 2**. The tested formulation shows advantages in either C_{max}, AUC_{0-12} and/or T_{max} values compared to the 'Control' formulation.

Formulation A1002 was selected for the preliminary human PK trial because its bioavailability parameters (C_{max} and AUC_{0-12}) were markedly superior to the Control formulation. T_{max}, however, was the same (2 hrs). This is significant when comparing the A1002 formulation with the known published data of the commercialized and FDA approved Epidiolex® product in which the T_{max} was measured between 4 to 5 hours post oral administration.

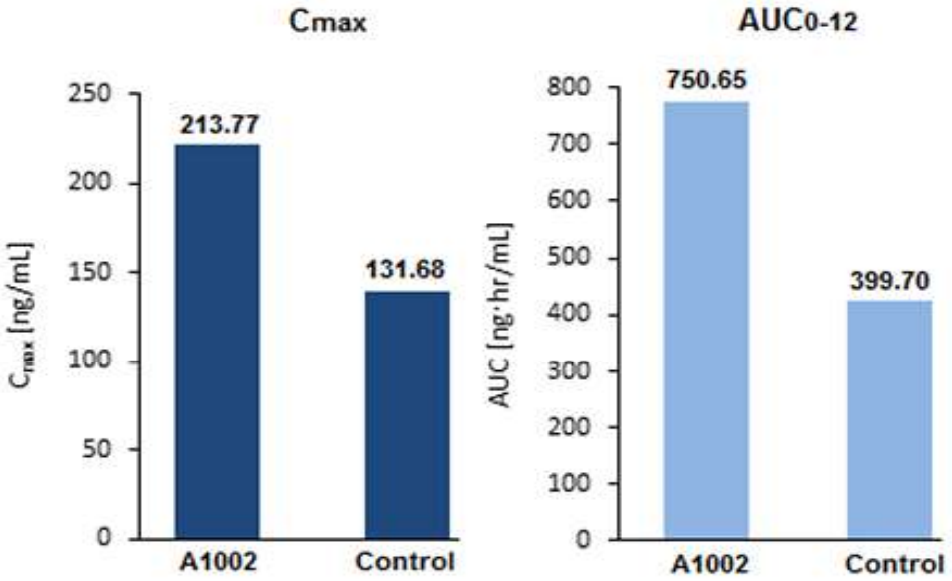


Figure 2 PK parameters for A1002 formulation

Table 3 CBD PK parameters and ratio of IP vs. Control

Formulation		T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-12} (ng*h/mL)
A1002N5S	Ave* [SD]	2.0 0.0	213.77 16.82	750.65 41.65
	Ratio**	1.00	1.62	1.88
Control	Ave* [SD]	2.0 0.0	131.68 4.76	399.70 11.46

*Ave: average, [SD]: Standard deviation
**Ratio: IP/Control

Overall Summary of pre-clinical Studies

The pharmacokinetic (PK) profile of the A1002N5S formulation was studied in rats. Sprague Dawley male rats (average weight 250 gr) received a single dose of 8 mg/kg (i.e., an average of 2.0 mg/animal) via gavage feeding. The CBD concentration of the formulation was 4.0 mg/mL. Blood samples for CBD plasma concentrations were collected at designated time points until 12 hrs after dosing. Six different formulations were evaluated and compared to a Control formulation (CBD in olive oil) at the same concentration. Of the 6 formulations 2 were selected, due to their unique PK parameters, as candidates for a preliminary human PK study; Formulation A1002N5S was selected because its bioavailability parameters (C_{max} and AUC_{0-12}) were markedly superior to the Control formulation (62% and 88% higher, respectively). T_{max}, however, was the same (2 hrs). This is significant when comparing A1002N5S to the known published data of the commercialized and FDA approved Epidiolex® product in which the T_{max} was measured between 4 to 5 hours post oral administration.

Clinical Pharmacokinetics of Orally Administered CBD

A systematic search of all articles reporting pharmacokinetic data of CBD in humans has been recently published (137). This review highlights the paucity in data and some discrepancy in the pharmacokinetics of cannabidiol, despite its widespread use in humans. The following sections

summarize the relevant available PK data for oral administration, including data from the Ananda safety and PK study conducted in Israel.

Absorption
Poor GI absorption and extensive hepatic first pass metabolism create significant barriers to oral bioavailability of CBD (which is usually low and erratic). Based on a review of available data, CBD's low bioavailability can be ascribed to incomplete gastrointestinal absorption coupled with extensive hepatic pre-systemic metabolism. Because CBD behaves as a high hepatic clearance compound, drug–drug interactions affecting its metabolism are likely to have a prominent impact on its systemic exposure after oral administration. There is a potential for developing improved CBD formulations with greater oral bioavailability and reduced susceptibility to food effects (138).

Distribution
CBD is a highly lipophilic compound and is readily taken up by adipose tissues and highly perfused organs such as the brain, heart, lung, and liver (91). Therefore, CBD has a large apparent volume of distribution; mean apparent volume of distribution (V/F [L]) was reported as 2,520 L following IV administration, and following single acute doses through oromucosal spray administration, the apparent volume of distribution was reported as 26,298, 31,994, and 28,312 L. In the Epidiolex® submission data (114), the estimated volume of distribution in healthy volunteers ranged from 20,963 L to 42,849 L. High plasma protein binding was observed for CBD and its metabolites (>94%).

Metabolism and drug-drug interactions (see section 2.4.1.2 *Risks of potential drug-drug interactions: Metabolism, P450 system and opioids*)

Elimination

Excretion: Fecal excretion is the major route of elimination of CBD and its metabolites [41]. Following a single oral dose of ^{14}C-CBD at 5 mg/kg, radioactivity was excreted predominantly via the fecal route (84%), and smaller proportions of administered radioactivity recovered in the urine (8%). The total recovery after 168 hours was 94% (114).

Half-life: The reported half-life ($t_{½}$) values of CBD appear to be inconsistent and depend on route of administration, formulation and probably other factors such as length of use, assay sensitivity, etc. The true elimination half-life of CBD may be difficult to calculate, as the equilibrium ratio plasma/fatty tissue is reached only slowly, resulting in very low plasma concentrations that are difficult to analyze.

Based on animal and human studies, elimination of oral cannabinoids from plasma is usually bi-phasic with an initial half-life ranging from approximately 1 to 3 hours, and the terminal elimination half-lives are in the order of 24 hours or longer (97, 114).

Human safety and PK study with A1002 formulation

The A1002 formulation (similar formulation to the A1002N5S Softgel Capsules) has been evaluated in a single-dose, three-way crossover study to assess the safety and pharmacokinetics of CBD in healthy volunteers. The study was conducted at Hadassah Clinical Research Center in Jerusalem, Israel (study AN-P-19-01). The test article was 5% synthetic CBD in the same excipient formulation as A1002N5S Softgel Capsules but diluted into water for oral ingestion rather than administered as a softgel capsule.

The trial, entitled A Single-Dose Three-Way Crossover Pilot Study to Assess the Safety and Pharmacokinetics of Cannabidiol (CBD) Following Oral Administration of Either a Novel Liquid

Nanodomains Formulation or a Reference CBD in Oil Preparation, to Healthy Volunteers, was conducted by Hadassah Clinical Research Center in Jerusalem, Israel (study AN-P-19-01).

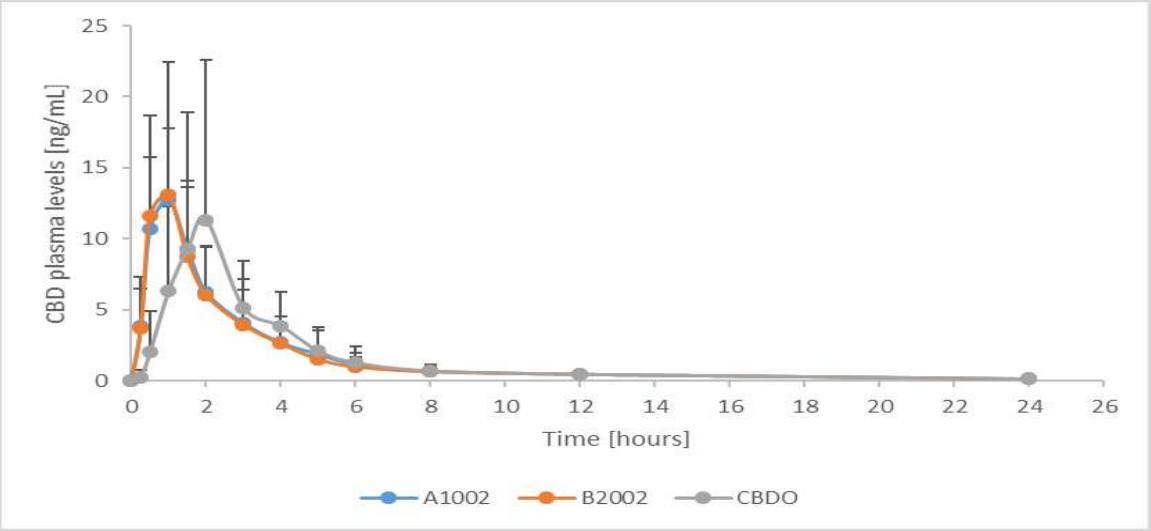
In this study, fifteen subjects were dosed at 50 mg of CBD and then monitored for safety and pharmacokinetics using the A1002N5S excipient nanodomain formulation with a CBD in olive oil as a reference. The CBD used for this study was synthetically produced. The subjects were dosed with a 1 mL formulation that was diluted with water to a 2% concentration and then taken orally. The study design was a single-dose, crossover study with a 7-day washout period between doses. All dosing was conducted in a fasted state (10 hr min). A summary of the PK data from this study is noted in Table 4.

Table 4 Oral Bioavailability Parameters from Healthy Volunteer Studies for the A1002 Formulation

Compound	Dose (mg)	Statistical Variable	T_{max} (hrs)[1]	C_{max} (ng/mL)[2]	AUC_{0-24} (ng*h/mL)[2]	AUC_{0-inf} (ng*h/mL)[2]	$T_{1/2}$ (hrs)
A1002	50	Mean (SD) SEM Median (range)	0.97 (0.50) 0.133 1.00 (0.50-2.00)	14.58 (4.79) 1.279 14.55 (7.30-24.36)	37.14 (16.26) 4.345 37.00 (18.80-80.54)	38.62 (16.62) 4.441 38.45 (19.72-82.99)	3.33 (0.96) 0.255 3.75 (1.99-4.54)
CBD in Oil (control)	50	Mean (SD) SEM Median (range)	1.72 (0.83) 0.221 1.75 (0.50-4.00)	13.05 (10.83) 2.893 9.79 (4.57-47.27)	36.00 (26.26) 7.018 26.48 (12.49 – 116.10)	37.49 (26.48) 7.076 27.92 (13.57-117.99)	3.27 (0.91) 0.243 3.22 (2.26-4.35)

The comparison of the PK profile for the A1002 formulation compared to the CBD in olive oil reference is shown as Figure 6.

Figure 6 PK profile of Two Nanodomain Formulations Compared to Reference



The Postulated Effect of the Formulation A1002N5S on GI Absorption of CBD

The structures within the formulation are self-assembled, thermodynamically stable, almost monodispersed and very small in size (10-50 nm). The formulation is based on non-ionic emulsifying agents (surfactants) that render CBD less susceptible to degradation or decomposition by the gastric fluid. Due to their small size, the droplets are spread over a significantly large surface area of the gut mucosa. The formulations contain phospholipids that enhance the mucosal enterocyte's membrane recognition of the droplets. The small micelle size of the nanoemulsion also promotes penetration of the mucus-rich "unstirred water layer" close to the intestinal wall, deeper between the intestinal villi.

The sesame oil nanodomains may enhance adherence to the surface membranes of mucosal enterocytes and so facilitate absorption. The CBD nanodomain in the sesame oil passes through the enterocytes into the mesenteric blood supply.

The improved contact with the surface of the GI mucosa due to the sesame oil facilitates the absorption of CBD and significantly shortens the time to maximum permeation of the drug (T_{max}). The improved surface area to volume facilitated by the surfactants results in enhanced bioavailability of CBD.

6.1.1 Acquisition

The investigational product, cGMP CBD, will be obtained from ANANDA Scientific with drug product shipped from the manufacturer located in the United States. A1002N5S Softgel Capsules will be manufactured by Baxco Pharmaceutical Inc., (California, USA) under cGMP conditions and shipped to NYULH.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Drug Substance and Excipients

A1002N5S Softgel Capsules will be administered as a 1 mL softgel capsule containing 50mg of pure CBD. The softgel capsule formulation will be supplied in white HDPE with child-resistant HDPE bottle caps. The clinical trial material will be packaged and labelled in compliance with the Good Manufacturing Practice for drugs used in clinical trials.

The formulation that was selected for the clinical trial contains CBD extracted from hemp (50 mg per capsule) and excipients as listed below:

Formulation A1002N5S

- Emulsifying agents: Cremophor EL (Polyoxyl 35 castor oil), Tween 80 (Polysorbate 80), Plurol® Oleique (polyglyceryl-3 dioleate);
- Co-surfactant: propylene glycol;
- Oil: sesame oil;
- Antioxidant: BHT (butylated hydroxytoluene).

Placebo Capsules

The placebo softgel capsule formulation will be composed of polysorbate 80, polyoxyl 35 castor oil, propylene glycol, plurol oleique CC 497, sesame oil, and BHT, in the same relative proportions as the A1002N5S Softgel Capsules. The softgel shell will be composed of gelatin, glycerin and purified water. The inactive ingredients in Ananda formulation A1002N5S have all been previously approved by the FDA for use as excipients in oral medications or food additives.

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

Storage conditions will be the same as those of the A1002N5S Softgel Capsules (protected from light and kept at controlled room temperature (20-25° C)).

6.1.3 Product Storage and Stability

The study drug (CBD or matching placebo) will be stored securely in the NYU-HHC Clinical Translational Science Institute (CTSI) located at Bellevue Hospital Center. A designated CTSI investigational pharmacist, in conjunction with the PI and designated study team members, will oversee the appropriate storage, accountability and dispensing of the study medication. Storage conditions for the A1002N5S Softgel Capsules will include: protected from light and kept at controlled room temperature (20-25° C).

Chemical and Physical Stability of the Liquid Nanodomains Formulation A1002N5S

Previous stability data of non-clinical batches have shown that the A1002N5S formulation is stable for at least 6 months at controlled room temperature. Based on the lack of degradation to date in the stability studies, it is likely that the shelf life of the softgel capsules will be extended to 12 months or longer.

The chemical stability of the A1002N5S formulation was evaluated at 25° C and 40° C for three months. No change in assay or impurities was detected.

The examination of the physical stability of CBD formulated in the liquid nanodomain systems was conducted using a rapid and efficient measurement termed LUMiFuge™ analytical centrifugation. This technique enables the prediction the physical stability and shelf life of a product. The liquid nanodomain formulations were shown to be stable at 3000 rpm and even after 17 hours of centrifugation. These conditions simulate the physical stability of the liquid nanodomains over minimum 2 years of storage and the results predict a shelf-life of at least two years based.

The PI will track expiration dates of each softgel capsule to assure that expired softgel capsules are not administered to participants. The PI will obtain additional un-expired drug product as necessary. Final chemical stability tests of the clinical batches will be reported in the Certificate of Analysis prior to commencement of the clinical trial.

6.1.4 Preparation

Because the investigational product (CBD or matching placebo) is going to be prepared by ANANDA Scientific and shipped to receive in its ready-for-dispensation formulation, there will not be any preparation required prior to dispensation. The study drug will be dispensed by qualified study personnel.

6.1.5 Dosing and Administration

Participants will self-administer CBD vs placebo twice daily for a total of 600mg/day CBD (***300mg po bid***) vs. placebo during the ***2-week*** pharmacologic treatment period. Participants will self-administer a quantity of 6 easy-to-swallow, soft gel capsules (each capsule containing either 50mg CBD or matching placebo with 0mg CBD), every morning following a light meal at approximately the same time of day, and an additional quantity of 6 capsules capsule approximately 6-12 hours later following a light meal.

6.1.6 Route of Administration

CBD or placebo will be administered orally in a liquid nanodomain formulation contained in soft gel capsules.

6.1.7 Starting Dose and Dose Escalation Schedule

All participants will receive 600mg/day CBD vs. placebo for 2 weeks of the pharmacologic treatment intervention period. Note: The first medication administration (CBD 300mg total, a total of 6 softgel capsules at 50mg; or placebo, 6 matching softgel capsules) will occur at visit Treatment 1 (T1). See ***section 6.3.1 Administration of Intervention*** section below for details.

6.1.8 Dose Adjustments/Modifications/Delays

If participants report AEs that are determined by the PI to be treatment-related during administration of study medication and are intolerable to the participant or represent a significant risk to the participant, daily administration will be reduced by 100-400mg/day every two days until symptoms are resolved or tolerable. Dose may be titrated back up toward the full dose as tolerated. Individuals who cannot tolerate the 600mg dose will remain on their maximum tolerable dose during the 2-week pharmacologic treatment period. Treatment will be discontinued immediately if continuing the medication places the participant at significant risk in the medical judgement of the PI.

6.1.9 Duration of Therapy

The duration of the active medication treatment portion of the study is 2 weeks.

6.2 Study Agent and Opioid Pharmacotherapy Accountability and Adherence Procedures

Because the study will use hemp derived CBD, this substance is not considered a controlled substance under the controlled substances act (CSA) as outlined in the 2018 Farm Bill. Therefore, there will be no need to obtain controlled substance research licenses from the New York State Bureau of Narcotic Enforcement or federal DEA.

The study drugs (CBD or matching placebo) will be stored securely in the NYU-HHC CTSI Investigational Pharmacy in designated areas within the CTSI located on the 4th floor of the CD Building at Bellevue Hospital Center. The CTSI Investigational pharmacy team, in conjunction with the PI and designated study staff, will oversee the appropriate storage, accountability and dispensing of the study medication to the participants.

Drug accountability related to study drug or placebo administration will be tracked using the ***Study Drug Dispensation/Accountability Log (BLINDED STUDY PERSONNEL)*** and ***Study Drug Participant Self-administration Log***. The ***Study Drug Dispensation/Accountablity Log (BLINDED STUDY PERSONNEL)*** records dispensation of study drugs to participants at treatment visits where study drug is to be dispensed (see **6.3.1 Administration of Intervention section** below for details). The information included in the Study Drug Dispensation Log is: 1) Subject ID; 2) Subject initials; 3) Dispensed by unblinded NYU CTSI pharmacist; 4) Received by blinded study team member; 5) Checked for accuracy (i.e., participant name, dispensation date, expiration date, number of capsules); 6) Visit Number; 7) Quantity dispensed; 8) Dispensed by PI or designee to participant; 9) Date and time dispensed. The ***Study Drug Participant Self-administration Log*** will be used to assess medication compliance by having participants record daily self-administration of study medication (CBD or placebo). The log will record: 1) subject initials and identification number; 2) date and time of study drug self-administration; 3) study medication (this will be listed as 'study medication' since participants will be blind to CBD or placebo); 4) number of capsules self-administered; and 5) whether they had food (light meal) prior to taking study medication. In addition, participants will use this log to record daily the use of prescribed opioid medication(s) and will record: 1) subject initials and identification number; 2) drug name; 3) dose of medication; 4) number of pills or capsules for oral medications; 5) date of administration; and 6) time of administration.

6.3 Study Behavioral or Social Intervention(s)

There will be no behavioral or social interventions as part of this trial.

6.3.1 Administration of Intervention

Over the treatment period of 2-weeks, participants will receive daily pharmacologic treatment with either CBD (600mg oral daily use) or an identical capsule containing placebo, also taken daily by mouth. The dosing regimen will be twice a day, approximately 12 hours apart with a light meal prior to taking the medications. Each capsule of active drug contains 50mg of CBD and so participants will be taking 6 pills on each dosing occasion for a total of 12 pills per day.

The first medication administration (either CBD 300mg total, a total of 6 softgel capsules at 50mg; or placebo, 6 matching softgel capsules) will occur at visit Treatment 1 (T1). At the end of clinic visit Treatment 1, participants will be provided with enough doses of CBD (50mg in each capsule) or placebo (12 doses of either CBD or placebo to take orally twice daily) to make it to the next session T2: 2-days after initiating pharmacologic treatment. Subsequently, CBD or placebo will be dispensed at each study visit (T2 & T3) to provide enough medication for ***twice daily*** (of either CBD 300mg or placebo) dosing prior to the next clinic visit (approximately 72-84 softgel capsules, respectively), until 2-weeks (T4).

Regarding visits T1-T4 (see section *2.4.1.2 Risks of potential drug-drug interactions: P450 system and opioids*), participants will be administered the first daily morning dose of medication (CBD 300mg, six 50mg capsules, or placebo) for that treatment period and will be evaluated for at least 3 hours at a **supervised clinical laboratory setting within the NYU-HHC Clinical & Translational Science Institute (NYU-HHC CTSI) at** Bellevue Hospital before discharge home. After administration of study drug or placebo until discharge for visits T1-T4, participants will be continuously monitored by the study physician or CTSI nursing staff. Participants will be monitored with safety assessments with particular attention directed to detect any signs of opioid intoxication or overdose (i.e., physical examination signs, vital sign monitoring including respiration and oxygenation). Vital signs (Blood pressure, pulse) will be obtained at a minimum of every 30 minutes by study staff or with increased frequency (including continuous monitoring) if clinically necessary. The use of continuous pulse oximetry monitoring will occur post administration of the study drug or placebo until discharge from the clinic to assess oxygenation status. The study physician will assess for clinical signs and symptoms suggestive of opioid intoxication or overdose (i.e., miosis, respiratory suppression, decreased oxygenation, sedation/lethargy), and will take appropriate medical steps to assure patient safety (i.e., Narcan administration, oxygen administration, inpatient hospitalization, breaking the blind, discontinuing study medication). The Richmond Agitation-Sedation Scale (RASS) (*see section 7.1.1 Study Specific Procedures for details*) will be used to assess clinician-rated somnolence or sedation. Participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test (one-leg stand, finger-finger test, Romberg's test, walk-and-turn task, and counting backwards) (129). If there are no AEs during this time period or lasting intoxicating effects of the study drug (e.g., participants are able to pass field sobriety tests several hours after study drug administration), participants will be dispensed the proper quantity of study drug (CBD or placebo) to self-administer daily at home until the next scheduled study visit (e.g., a 1-day, 6-day, or 1-week supply, depending on the visit).

6.3.2 Procedures for Training Interventionalists and Monitoring Intervention Fidelity

Not applicable.

6.3.3 Assessment of Subject Compliance with Study Intervention

The Study Drug Participant Self-Administration Log will be used to assess medication compliance by recording daily self-administration of study medications. Plasma concentrations of CBD will also be collected at T1-T4 visits and will be an additional assessment to verify treatment adherence. All treatment sessions, assessments, data entry, and analysis will be performed at the NYU-HHC CTSI at Bellevue Hospital Center.

6.4 *Study Procedural Intervention Description Table 1: Study Endpoints/Assessments*

6.4.1 *Administration of Procedural Intervention/ Schedule of Assessments*

Study Phase	Screen	Baseline	(Rx[1])	Rx	Rx	Rx
Study Visit	S1, 2, 3	B1	1	2	3	4
Target Weeks	-6 to -2	-2 to 0	1-day	2-day	1 (-2d)	2 (-2d)
Time		T0	T1	T2	T3	T4
Inclusion/Exclusion Criteria						
COVID-19 Screening	X	X	X	X	X	X
Screening Checklist	X					
Informed Consent (ICF)	X					
ICF Comprehension Quiz	X					
ICF Documentation	X					
Authorization for Release of Health Information	X					
Confidential Contact Information	X					
Demographics (PhenX Tier-1)	X					
Medical/Psychiatric History	X					
SCID-5	X					
Alcohol Test	X					
Physical Examination	X					
Clinical Labs	X				X[2]	X[2]
EKG	X					
Birth Control Documentation	X	X	X		X	X
Urine Pregnancy Test	X	X	X	X	X	X
Urine Drug Screen	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Eligibility (I/E) Checklist	X	X				
Randomization		**X**				
CBD/PCB Dispensed			X[3]	X[3]	X[3]	X[3]
Safety Assessments						
Vital Signs	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Suicidality (C-SSRS)	X	X	X	X	X	X
Sedation (RASS)			X	X	X	X
Field Sobriety Tests			X	X	X	X
Pharmacokinetics						
CBD Plasma Levels			X[5]	X[4,5]	X[4,6]	X[4,5]
Opioid Plasma Levels		X	X[4]	X[4]	X[4]	X[4]
Opioid—Related Outcomes						
Opioid Maintenance Dose (MEDD)	X	X	X		X	X
Opioid Craving (VAS)		X	X	X	X	X
Secondary Efficacy Outcome: Pain Outcomes						
Brief Pain Inventory (BPI)		X	X	X	X	X
Pain Catastrophizing Scale (PCS)		X	X	X	X	X
Mental Health Outcomes						
Anxiety (PROMIS)		X	X	X	X	X
Depression (PROMIS)		X	X	X	X	X
Sleep (PROMIS)		X	X	X	X	X
Blinding Integrity						**X**
Self-Administration Medication Log	**X**	**X**	**X**	**X**	**X**	**X**
Participant Compensation	**X**	**X**	**X**	**X**	**X**	**X**

[1]Rx= Pharmacologic Treatment Period [2]Liver function tests
[3]Study medication or placebo dispensed at visit for daily use until the next visit
[4]Blood drawn before starting CBD/PCB administration (0hr)
[5]Blood draws after starting CBD/PCB administration (1hr/3hr)
[6]Blood draws after starting CBD/PCB administration (1hr/3hr/5hr)

Refer to **Table 1** for study timeline and assessments. Measures assessed at each time point are described below. The eligibility checklist will be completed at the screening and baseline visits, followed by randomization to pharmacologic treatment of daily oral administration of drug (**CBD 600mg or placebo**) for **2-weeks**. Clinic visits will occur at baseline and then post-randomization/initiation of pharmacologic treatment at the following time-points: 1-day (note: this represents the first day of drug administration), 2-day, 1-week, and 2-weeks.

6.4.2 Procedures for Training of Clinicians on Procedural Intervention

Not applicable.

6.4.3 Assessment of Participant Compliance with Study Procedural Intervention

See Section 6.3.3 above: **Assessment of Subject Compliance with Study Intervention**

7 Study Procedures and Schedule

7.1 *Study Procedures/Evaluations*

7.1.1 Study Specific Procedures

Refer to **Table 1** for study timeline and assessments. Measures assessed at each time point are described below.

Following obtaining informed consent (including informed consent comprehension quiz and documentation of informed consent), the following will occur to determine study eligibility:

- Authorization of release of health information will be obtained in order to obtain relevant health information, in particular as it relates to establishing the inclusion criteria of participants with chronic radiculopathic pain syndromes maintained on chronic opioid therapy. All efforts will be made to obtain necessary health information from relevant treatment providers (i.e., pain specialists, internists).

- A Locator form and PhenX Tier 1 measures will completed at screening to collect contact information, demographics, quality of life, HIV risk and status, and substance use measures (age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco, and other substances; www.phenxtoolkit.org).

- Medical screening will include height, weight, medical and psychiatric history, physical examination, complete blood count, serum chemistries including liver function tests (LFTs), serum pregnancy test, urinalysis, urine drug test, urine pregnancy test, concomitant medications assessment, and administration of an EKG. Note: Urine drug screenings, urine pregnancy tests, and birth control method documentation will be administered to assess recent drug use and to assess pregnancy status (in addition to screening) at all study visits, and follow-up LFTs will be obtained at 1-week and 2-weeks following initiation of pharmacologic intervention. Regarding the urine drug assessment at screening, the data will be used to determine eligibility (i.e., if consistent with an exclusionary substance use disorder assessed also with SCID-5; if consistent with exclusionary recreational or medicinal cannabis use). The licensed provider will also review participants' controlled substance prescription history using the online Prescription Monitoring Program (PMP) ISTOP Registry in New York to inform study eligibility.

- Psychiatric and substance use disorder (SUD) screening will occur including administration of the Structured Clinical Interview for DSM-5 (SCID-5) Research

Version/Non-patient (SCID-RV/NP for DSM-5®) Version 1.0.0 (139) to determine exclusionary psychiatric and SUD diagnoses. Note: Only relevant sections (mood disorders, psychotic disorders, and substance use disorders) to determine eligibility will be administered to participants during screening.

Safety

Safety will be assessed by collection of adverse events and vital signs at all visits after treatment is initiated. Safety will be assessed by collection of adverse events using the Systemic Assessment for Treatment of Emergent Events (SAFTEE) (140) measure at all visits after treatment is initiated. LFTs will be obtained at screening, 1-week, and 2-weeks following initiation of pharmacologic intervention. Any subject who has LFTs > 2 x ULN will be discontinued from study participation and will be referred for appropriate follow-up. Following screening, urine drug assessments will be collected at every subsequent study visit, T0-T4. The results of the urine drug assessments will be evaluated to determine ongoing safety of study participation (i.e., potential adverse drug-drug interactions) and continued study eligibility. For instance, if the urine drug assessment(s) reveal evidence for a prior (that was not detected at screening) or new onset exclusionary substance use disorder, the participant will be deemed no longer eligible for study participation. If a participant is no longer eligible for study participation because they have an exclusionary substance use disorder, the PI (a substance abuse expert) will refer the participant for appropriate substance abuse and mental health treatment.

Risk of suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (131) as part of each study visit, including screening and baseline. There are two version of the C-SSRS that will be used: one for 'screening or baseline' and one 'since last visit' version.

See ***Section 2.4.1 (Known Potential Risks and Risk Mitigation Strategies) above*** for safety plan to mitigate risk related to potential drug-drug interactions between CBD and other drugs (i.e., opioids). The Richmond Agitation-Sedation Scale (RASS) will be used to measure clinician-rated somnolence or sedation. The RASS is a 10-point scale with four levels to describe the agitated patient (+1 to +4), one level to describe the calm and alert patient (0) and another five levels to describe a sedated patient (-1 to -5) (141, 142). The rating is performed in three steps (observation, response to verbal stimulation and response to physical stimulation), is user friendly, and can be performed quickly. The RASS is one of the most frequently used sedation scales (143) and has been demonstrated to be both valid and reliable (141, 144). It is an appropriate scale to measure clinically significant somnolence associated with opioid intoxication.

Pharmacokinetics: Plasma opioid and CBD concentrations

Opioid analgesic plasma concentrations will be obtained at baseline (prior to initiating pharmacologic treatment) by taking 2 samples over an approximately 2-week period prior to initiating the pharmacologic intervention at T1. Note: the baseline plasma levels will be drawn at the same time relative to when they take their opioid medication(s). The baseline opioid plasma value will be the average of the two samples taken during this period of time (with one sample during the period between baseline and T1 and the 2nd sample taken at the beginning of T1 prior to initiating the first pharmacologic intervention). Further PK samples will be drawn at the following time points (post-randomization and after receiving the first dose of study medication): 2-day (T2), 1-week (T3), and 2-weeks (T4), and these will also be drawn at the same time relative to when they take their opioid medication(s). At these assessment time-points: 1) Opioid plasma concentrations will be sampled, using the same methodology used to obtain the baseline plasma level; 2) CBD plasma concentrations will be obtained as well. Trough CBD concentrations will be sampled at the same time that the opioid plasma concentration will be assessed and subsequently within the first several hours after

CBD/placebo administration with samples drawn at approximately 1-hour and 3-hours post CBD/placebo administration during visits (T1-T4) at the CTSI, with an additional sample taken 5-hours post CBD administration during the T3 visit. To minimize the number of blood draws at these assessment time-points, an IV catheter will be placed to obtain the 3-4 blood samples.

Plasma CBD and opioid concentrations will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) by a laboratory at the University of Buffalo.

Pain Outcomes

Pain Catastrophizing: Pain catastrophizing will be measured by the Pain Catastrophizing Scale (***PCS***) (132) at baseline and the following post-randomization time-points: 2-day, 1-week, and 2-weeks. The PCS is a 13-item self-report scale, with each item rated on a 5-point scale: 0 (Not at all) to 4 (all the time). It is broken into three subscales (magnification, rumination, and helplessness); results observational and treatment outcome trials have suggested that the PCS has very good prognostic value in assessing pain outcomes in patients with chronic pain syndromes (145-148).

Pain Intensity and pain-related interference: The severity of chronic pain will be evaluated with the Brief Pain Inventory (***BPI***) (133, 149) at baseline and the following post-randomization time-points: 1-day, 2-day, 1-week, and 2-weeks. The BPI has two dimensions: intensity and interference. Pain intensity is rated on a 0 (no pain) to 10 (worst pain imaginable) scale as the worst in the past 24 hours, least in the past 24 hours, average pain and current pain. Pain interference is measured in 7 areas: general activity, mood, walking ability, work, sleep, enjoyment of life and relationships on a 0 (no interference) to 10 (interferes completely) scale. The composite mean of these scores are used as a pain interference score.

Mental Health Outcomes

Anxiety will be measured with the 29-item PROMIS® (134) (Patient-Reported Outcomes Measurement Information System) Anxiety long form scale, assessed at baseline and the following post-randomization time-points: 1-day, 2-day, 1-week, and 2-weeks.

Depression will be measured with the 8-item PROMIS® (134) (Patient-Reported Outcomes Measurement Information System) Depression short form scale, assessed at baseline and the following post-randomization time-points: 1-day, 2-day, 1-week, and 2-weeks.

Sleep Disturbances will be measured with the 27-item PROMIS® (Patient-Reported Outcomes Measurement Information System) Sleep-Related Impairment (SRI) (135), at baseline and the following post-randomization time-points: 1-day, 2-day, 1-week, and 2-weeks.

Opioid Use-Related Outcomes

Opioid Craving will be measured with the Visual Analog Scale (***VAS***) (136), (150) at baseline, 1-day, 2-day, 1-week, and 2-weeks.

Opioid maintenance dose (measured in MEDD): assessed at screening, baseline, 1-day, 1-week, and 2-weeks.

- MEDD will be calculated using 2 reference documents**:**
    - Guideline and conversion table to calculate MEDD from Centers for Medicaid and Medicare Services (CMS)
    - Guidelines from the Centers for Disease Control and Prevention (CDC) intended for calculating total daily dose of opioids for safer dosage of opioid pharmacotherapy

7.1.2 Standard of Care Study Procedures

Participants will continue to get standard of care treatment for their chronic radicular pain syndromes. In addition, as part of participation in this clinical trial, participants will receive additional medical attention and care as part of a clinical research program (i.e., physical exam, laboratory analyses, clinical assessments, administration of study medications, longitudinal assessments).

7.2 *Laboratory Procedures/Evaluations*

7.2.1 Clinical Laboratory Evaluations

Serum will be collected at screening for: complete blood count, pregnancy test, and serum chemistries including liver function tests (LFTs). Further, in addition to obtaining baseline liver function tests (LFTs), after initiating study medication or placebo, subsequent LFTs will be obtained at 1-week and 2-weeks (final study visit). Opioid analgesic plasma concentrations will be collected at the same time relative to when participants take their daily opioid analgesic medications at baseline (prior to initiating pharmacologic treatment) and at the following post-randomization/post-start of study medication administration visits: 1-day, 2-day, 1-week, and 2-weeks. CBD plasma concentrations will be obtained at all study visits (1-day, 2-day, 1-week, and 2-weeks) following initiation of study drug administration and will occur at the following time assessment points at these visits: trough (pre-dose), 1-hour post drug-administration, and 3-hours post drug administration.

7.2.2 Other Assays or Procedures

See section 7.2.1

7.2.3 Specimen Preparation, Handling, and Storage

Plasma (~1ml/sample) will be stored at -70° C, and will be labeled with study number, participant number, visit number, and time-point. Plasma CBD concentrations will be determined via High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) and plasma opioid concentrations will be quantified by highly sensitive enzyme linked immunosorbent assay (ELISA) kits by a laboratory at the University of Buffalo.

7.2.4 Specimen Shipment

Specimens will be shipped at a minimum of every 6 months on dry ice with appropriate labeling for shipment of biological specimens on dry ice, according to the study's SOP. Opioid and Cannabinoid Plasma Case Report Form will be utilized to record dates and times that each specimen was collected and shipped. Specimens may be shipped overnight between 9:00am and 5:00pm on business days.

7.3 Study Schedule

7.3.1 Screening

Screening Visit (S1-3)

- Screening Visit Checklist
- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
    - Obtain informed consent comprehension quiz. Participant must pass the quiz in order to be eligible for the study
    - Document informed consent process including comprehension quiz
    - Provide participant with a copy of the informed consent
- Obtain authorization of release of health information (e.g., to speak to treating pain and opioid treatment provider(s) or other relevant health care providers)

- Obtain demographic information, drug, alcohol, and tobacco use history
- Review medical and psychiatric history to determine eligibility based on inclusion/exclusion criteria.
- Review concurrent medications to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Collect urine for urine drug analysis, urinalysis, urine pregnancy test
- Collect blood (~10cc, or about 2 teaspoons) for complete blood count, serum chemistries including LFTs, and serum pregnancy test
- Record results of evaluations of safety and opioid-use related outcomes
- Provide participant with Medication Self-Administration Log for tracking opioid medication self-administration, to be used for particular opioid's plasma level and future plasma draw scheduling
- Schedule additional Screening Visits (S2/S3) if necessary, as per PI discretion
- Schedule study visits for participants who are eligible and available for the duration of the study

7.3.2 Enrollment/Baseline

Enrollment/Baseline Visit: T0

- Collect urine for urine drug analysis and urine pregnancy test
- Record vital signs, results of examinations, and other assessments
- Review concurrent medications
- Record results of evaluations of safety, pain outcomes, mental health outcomes, and opioid-use related outcomes
- Pharmacokinetic assessment: Collect 1 blood sample (1 or 2 tablespoons) over an approximate 2 week period prior to T1
- Record adverse events as reported by participant or observed by investigator
- Note: this visit will occur over approximately 2-weeks prior to visit T1

7.3.3 Intermediate Visits

7.3.3.1 1-day (first day of pharmacologic treatment): T1

- Collect urine for urine drug analysis and urine pregnancy test
- Record vital signs, results of examinations, and other assessments
- Review concurrent medications
- Record results of evaluations of safety outcomes
- Record results of evaluations of safety, pain outcomes, mental health outcomes, and opioid-use related outcomes
- Pharmacokinetic assessment at NYU-HHC CTSI prior to administering first dose of CBD 300mg or placebo: after establishing an IV heplock for the three blood samples to be drawn for PK assessments, collect 1 blood sample (1 or 2 tablespoons). This assessment will be averaged with the opioid plasma concentration sample taken during the baseline period to form the baseline opioid plasma concentration.
- Administer first dose of CBD 300mg or placebo in the NYU-HHC CTSI after a light meal
- Pharmacokinetic assessment at NYU-HHC CTSI subsequent to administering first dose of CBD 300mg or placebo: collect 2 blood samples (1 or 2 tablespoons each) approximately 1-hour and 3-hours after administering CBD 300mg or placebo, respectively.
- Monitor closely for a minimum of 3 hours for safety (i.e., signs and symptoms suggestive of opioid toxicity) prior to discharge home

- Record adverse events as reported by participant or observed by investigator
- Record participant's adherence to treatment program
- Participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test
- At the end of clinic visit T1, participants will be provided with enough doses of CBD 50mg/dose or placebo (12 doses total) to take CBD 300mg or placebo orally twice daily, following a light meal, to make it to the next session T2: 2-days after initiating pharmacologic treatment. Note: of these 12 doses, participants will take 6 of them for the nighttime dose in between T1 and T2. The remaining 6 doses will be brought into the CTSI for the am dose at the T2 visit.

7.3.3.2 2-day (second day of pharmacologic treatment): T2

- Collect urine for urine drug analysis and urine pregnancy test
- Record vital signs, results of examinations, and other assessments
- Review concurrent medications
- Record results of evaluations of safety outcomes
- Record results of evaluations of safety, pain outcomes, mental health outcomes, and opioid-use related outcomes
- Pharmacokinetic assessment at NYU-HHC CTSI prior to administering first daily dose of CBD 300mg or placebo: after establishing an IV heplock for the three blood samples to be drawn for PK assessments, collect 1 blood sample (1 or 2 tablespoons) to assess both opioid plasma and CBD trough plasma concentrations.
- Administer first dose of CBD 300mg or placebo in the NYU-HHC CTSI after a light meal
- Pharmacokinetic assessment at NYU-HHC CTSI subsequent to administering first daily dose of CBD 300mg or placebo: collect 2 blood samples (1 or 2 tablespoons each) approximately 1-hour and 3-hours after administering CBD 300mg or placebo, respectively.
- Monitor closely for a minimum of 3 hours for safety (i.e., signs and symptoms suggestive of opioid toxicity) prior to discharge home
- Record adverse events as reported by participant or observed by investigator
- Record participant's adherence to treatment program
- Participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test
- At the end of clinic visit T2, participants will be provided with enough doses of CBD 50mg/dose or placebo (72 doses total) to take CBD 300mg or placebo orally twice daily, following a light meal, to make it to the next session T3: 1-week after initiating pharmacologic treatment. Note: participants will bring in the final 6 doses into the CTSI for the am dose at the T3 visit.

7.3.3.3 1-week: T3

- Collect urine for urine drug analysis and urine pregnancy test
- Record vital signs, results of examinations, and other assessments
- Review concurrent medications
- Record results of evaluations of safety outcomes
- Record results of evaluations of safety, pain outcomes, mental health outcomes, and opioid-use related outcomes
- Collect blood for LFTs (approximately 1 teaspoon)
- Pharmacokinetic assessment at NYU-HHC CTSI prior to administering first daily dose of CBD 300mg or placebo: after establishing an IV heplock for the four blood samples to be

drawn for PK assessments, collect 1 blood sample (1 or 2 tablespoons) to assess both opioid plasma and CBD trough plasma concentrations.
- Administer first daily dose of CBD 300mg or placebo in the NYU-HHC CTSI after a light meal
- Pharmacokinetic assessment at NYU-HHC CTSI subsequent to administering first daily dose of CBD 300mg or placebo: collect 3 blood samples (1 or 2 tablespoons each) approximately 1-hour, 3-hours, and 5-hours after administering CBD 300mg or placebo, respectively.
- Monitor closely for safety (i.e., signs and symptoms suggestive of opioid toxicity)
- Record adverse events as reported by participant or observed by investigator
- Record participant's adherence to treatment program
- Participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test
- At the end of clinic visit T3, participants will be provided with enough doses of CBD 50mg/dose or placebo (84 doses total) to take CBD 300mg or placebo orally twice daily, following a light meal, to make it to the next session T4: 2-week after initiating pharmacologic treatment. Note, participants will bring in the final 6 doses into the CTSI for the am dose at the T4 visit.

7.3.4 Final Study Visit at 2-weeks: T4

- Collect urine for urine drug analysis and urine pregnancy test
- Record vital signs, results of examinations, and other assessments
- Review concurrent medications
- Record results of evaluations of safety outcomes
- Record results of evaluations of safety, pain outcomes, mental health outcomes, and opioid-use related outcomes
- Collect blood for LFTs (approximately 1 teaspoon)
- Pharmacokinetic assessment at NYU-HHC CTSI prior to administering first daily dose of CBD 300mg or placebo: after establishing an IV heplock for the three blood samples to be drawn for PK assessments, collect 1 blood sample (1 or 2 tablespoons) to assess both opioid plasma and CBD trough plasma concentrations.
- Administer first daily dose of CBD 300mg or placebo in the NYU-HHC CTSI after a light meal
- Pharmacokinetic assessment at NYU-HHC CTSI subsequent to administering first daily dose of CBD 300mg or placebo: collect 2 blood samples (1 or 2 tablespoons each) approximately 1-hour and 3-hours after administering CBD 300mg or placebo, respectively.
- Monitor closely for safety (i.e., signs and symptoms suggestive of opioid toxicity)
- Record adverse events as reported by participant or observed by investigator
- Record participant's adherence to treatment program
- Participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test
- To evaluate the effectiveness of the blind, both treatment and investigator treatment assignment guesses (i.e., whether participant received investigational drug vs placebo) will be collected

7.3.5 Withdrawal/Early Termination Visit

If the subject withdraws or if early termination occurs, the following procedures/evaluations would be ideal to obtain at a final study visit: safety assessments, pain outcomes, mental health outcomes, and opioid-related outcomes.

7.3.6 Unscheduled Visit

Unscheduled visits will be documented on an unscheduled visit form.

7.4 *Concomitant Medications, Treatments, and Procedures*

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 *Justification for Sensitive Procedures*

This trial employs a double-blind methodology as part of the pharmacologic intervention. The study drug (CBD) will be formulated in identical and blinded capsules to the inactive placebo agent. The double-blind methodology aims to reduce investigator and participant biases. To evaluate the effectiveness of the blind, both participant and investigator treatment assignment guesses (i.e., whether received investigational drug vs placebo) will be collected at the following time-points (post-initiation of pharmacologic treatment): 4-weeks (T4), and 16-weeks (T8) (***See section 10.6.2 Evaluation of Success of Blinding).***

7.5.1 Precautionary Medications, Treatments, and Procedures

Participants currently using the following concomitant medications will be excluded from study participation: 1) medications (including opioid analgesics) metabolized primarily by CYP2C19 isoenzymes; 2) medications significantly or primarily metabolized by CYP3A4 with the potential for adverse drug-drug interactions with CBD (i.e., ketoconazole, rifampicin). We will instruct participants to subjects to avoid consuming grapefruit or grapefruit juice during the duration of the study; 3) medications known to have adverse drug-drug interactions with CBD (i.e., valproate) or the potential to cause significant drug-drug interactions (i.e., clobazam); 4) recreational or medical cannabis or any product containing CBD.

7.6 *Prohibited Medications, Treatments, and Procedures*

See Section 7.5.1 above.

7.7 *Prophylactic Medications, Treatments, and Procedures*

Participants will receive study medication (CBD or placebo) on top of standard of care treatment for chronic radiculopathy pain syndromes. Concomitant medication use will be tracked closely throughout the trial for safety/risk assessments.

7.8 *Rescue Medications, Treatments, and Procedures*

Regarding visits T1-T4, participants will be administered the first daily morning dose of medication (CBD 300mg or placebo) with food for that treatment period and will be evaluated for several hours at a supervised clinical laboratory setting within the NYU-HHC Clinical & Translational Science Institute (NYU-HHC CTSI) at Bellevue Hospital. Participants will be closely monitored with safety assessments with particular attention directed to detect any signs of opioid intoxication or overdose (i.e., physical examination signs, vital sign monitoring including respiration and oxygenation). If participants develop clinical signs and symptoms suggestive of opioid intoxication or overdose (i.e., respiratory suppression, decreased oxygenation, lethargy), they will be immediately evaluated clinically and appropriate medical steps will be taken to assure patient safety (i.e., Narcan administration, oxygen administration, inpatient hospitalization, breaking the blind, discontinuing study medication). Participants will not be permitted to leave the study site until they are able to pass a standard field sobriety test (one-leg stand, finger-finger test, Romberg's test, walk-and-turn task, and counting backwards)

(129). The PI will use clinical discretion in the event that a participant cannot complete the field sobriety test due to disability.

Per July 2020 FDA drug safety communication (https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-health-care-professionals-discuss-naloxone-all-patients-when-prescribing-opioid-pain), the study team will communicate with all clinicians prescribing opioids to subjects enrolled in study that they provide a naloxone prescription for each participant.

7.9 *Participant Access to Study Agent at Study Closure*

Participants will not be able to access investigational study medication (CBD) used in this trial beyond the 2-week treatment period.

8 Assessment of Safety

8.1 Specification of Safety Parameters

Safety and toxicity monitoring will be performed throughout the study for all participants. Safety variables to be assessed include AEs, vital signs, and safety laboratory values, when collected.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. At each study visit following screening, designated study team members will inquire about the occurrence of AE/SAEs since the last visit.

Since the GI disturbance of diarrhea is one of the most common adverse effects attributed to CBD, diarrhea will be queried as an AE of special interest in this trial.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** (SAE) is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse,

a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 *Classification of an Adverse Event*

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to the study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g.,, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g.,, the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g.,, the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g.,, the participant's clinical condition, other concomitant treatments)

- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

Unexpected: An AE is considered unexpected if it is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed, or not previously observed in animal toxicity studies for CBD. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacologic properties of the drug, but are not specifically mentioned as occurring with CBD.

8.3 *Time Period and Frequency for Event Assessment and Follow-Up*

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition

deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 *Reporting Procedures – Notifying the IRB, FDA, DSMB*

8.4.1 Adverse Event Reporting

To the IRB: In accordance with local IRB requirements, all AEs occurring during the course of the clinical trial regardless of relationship to study activities will be collected, documented, and reported by the PI or designee to the IRB o*n an annual basis* in the application for the study's continuation renewal. Staff education, re-training or appropriate corrective action plan will be implemented when unreported or unidentified AEs or SAEs are discovered, to ensure future identification and timely reporting.

To the FDA: In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the PI or IND Sponsor. *On an annual basis,* as part of the update to the study IND, the IND Sponsor will submit to the FDA:

- A list of all AEs that have occurred during the reporting period
- A summary of all IND safety reports submitted during the past year
- A list of all subjects who died during the participation in the investigation, listing cause of death for each,
- And a list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

To the DSMB: All AEs occurring during the course of the clinical trial, regardless of relationship to study activities, will be reported to the DSMB at regular meetings. Prior to each DSMB meeting, the PI will prepare a report to the Board including review of aggregate analysis of AEs and SAEs.

Following each meeting, the board will provide the PI with a report including a recommendation to continue the study unchanged, continue with modifications of the protocol and/or the consent form to protect participant safety, or terminate the study. This report will then be submitted to the FDA as part of the annual report to the study IND, and the IRB in the application for the study's annual continuation renewal.

To the Study Investigational Product Provider: ANANDA Scientific

The PI shall promptly inform ANANDA Scientific of any significant safety issues occurring during the course of the study that might affect the performance of the study and of any AEs and SAEs experienced by subjects during the study. The PI shall share with ANANDA Scientific any associated CRFs and source data, safety reports related to such AEs and SAEs, and permit access to anonymized pharmacokinetic data of study subjects.

To NIH/NIDA

All AEs occurring during the course of the clinical trial regardless of relationship to study activities will be collected, documented, and reported by the PI or designee to NIH/NIDA on an annual basis in the annual Research Performance Progress Report (RPPR).

8.4.2 Serious Adverse Event Reporting

SAEs will be promptly reported to the Clinical Research Coordinator and PI. The PI or qualified designee will distinguish Serious Adverse Events (SAEs) from Adverse Events (AEs). The details of the event will be documented and reported as follows:

To the FDA: The PI is required to report certain study events in an expedited fashion to the FDA. These written notifications of AEs are referred to as IND/IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected, and
  - fatal or life-threatening
- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous AE that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Each written notification must be submitted on an FDA Form 3500A. The PI is also required to identify in IND safety reports all previous reports concerning similar AEs and to analyze the significance of the current event in light of the previous reports.

FDA contact for reporting IND safety reports

Rachel Jang, PharmD, Regulatory Project Manager at Rachel.Jang@fda.hhs.gov or Rigoberto Roca MD, Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine, Office of Neuroscience, FDA Center for Drug Evaluation and Research.

To the IRB: The IRB Chair or Administrator will be notified immediately for SAEs that are at least possibly related to study participation only. If the IRB administrator determines that reporting of the incident/issue is required, it will be submitted to the IRB within 48 hours of the IRB direction/response.

The team will also submit summary information related to all SAEs, AEs, and UPs in the annual application for continuation to the IRB.

To the Study Sponsors:

NIH/NIDA

All SAEs will be documented and reported to NIDA within 72 hours with copies included in the participant's file.

CBD drug manufacturer: ANANDA Scientific

If an SAE occurs after the subject signs informed consent through the end of study participation, the PI or a qualified designee will complete the SAE Form and send it via email to contacts designated by ANANDA Scientific within 48 hours of the site becoming aware of the SAE. The form must be completed and submitted to ANANDA Scientific any time a serious medical event has occurred in a participant during the clinical trial, whether or not it is considered related to the study treatment, including active comparators and placebo.

DSMB

All SAEs will be documented and reported to the DSMB within 72 hours with copies included in the participant's file.

Ensure that an investigator has reviewed and signed the SAE form prior to submission.

Every exposure during pregnancy (participant) should be reported on an SAE worksheet as a case of special interest from the time of study enrolment to the end of study participation.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs involving risks to subjects or others require notification of the local IRB. The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. Any incident, experience, or outcome that meets all of the following criteria is considered to be Reportable New Information (RNI) and is required to be promptly reported to the local IRB:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means that, in the opinion of the PI, the incident, experience, or outcome was more likely than not caused by procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

The RNI report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

UPs must be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor according to SAE reporting procedures described above (within 48 hours of the investigator becoming aware of the event).
- UPs that meet the requirements for RNI will be reported to the IRB as soon as possible and within 5 working days of the site becoming aware of the event.
- All other UPs not related to study activities or that do not result in harm to participants will be reported to the IRB annually in the application for the study's continuation renewal.

8.4.4 Reporting of Pregnancy

Pregnancy information on clinical study subjects is collected by the investigator. If a subject should become pregnant during the course of the study, the investigator or qualified designee will contact the IRB and ANANDA Scientific within 5 working days of the PI or qualified designee first becoming aware of the pregnancy.

Pregnancies resulting in congenital abnormalities or birth defects in offspring meet the requirements for an SAE and will be collected, documented, and reported according to the procedures outlined above for SAEs.

8.5 *Reporting Procedures – Notifying the Study Sponsor*

Not applicable as PI is the sponsor-investigator

8.6 *Reporting Procedures – Notifying the FDA*

See section ***8.4.2 Serious Adverse Event Reporting***

8.7 *Reporting Procedures – Participating Investigators*

Not applicable.

8.8 *Study Halting Rules*

The study may be stopped if there are untoward and concerning levels of AE or SAE outcomes attributable to CBD or study participation. If the DSMB finds it is likely that CBD is contributing to negative outcomes, they will consider solutions including protocol changes or potentially stopping the study. Anticipated AEs of concern will be opiate overdose, respiratory suppression, and greater than 3x increase in ALT and AST. All SAEs will be documented and reported to the DSMB within 72 hours for review.

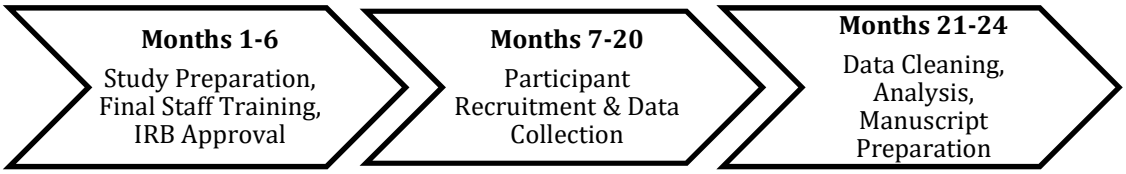
8.9 Safety Oversight: DSMP

Data and Safety Monitoring Plan (DSMP)
Title: A phase I/II, randomized, double-blind, placebo-controlled, single-center study of the effects of Cannabidiol (CBD) on opioid plasma levels in participants with chronic radiculopathies maintained on chronic opioid therapy (COT)

Grant Number: R21DA048986-01

PI: Stephen Ross MD

Medical Monitor: Stephen Ross MD



- All significant changes to the protocol must be approved by the NIDA Program Officer prior to implementation.
- All SAEs must be reported to NIDA/NIH within 72 hours.
- An annual DSMP report will be sent to NIDA/NIH.

Brief description of the protocol: *see section 4 Study Design and Endpoints*

Primary and secondary outcome measures: *see section 4 Study Design and Endpoints*

Inclusion/exclusion criteria: see section 5 Study Enrollment and Withdrawal

Sample size: *see section 10.5 Sample Size*

List of participating enrolling clinics or data collection centers: *see section 5 Study Enrollment and Withdrawal*

Projected timetable: *see R21 enrollment projections graph above*

Target population distribution (e.g., women, minorities)

Inclusion of Women

Participants will not be excluded based on gender. However, there are sex differences between men and women among opioid-abusing chronic pain patients. Women are more likely to be prescribed opioids than men, more likely to take higher daily doses (151, 152) and are at higher risk for opioid-related overdoses leading to hospitalization (153). It is expected that at least 50% of the participants in this trial will be women.

Inclusion of Minorities

No participants will be excluded because of ethnic or racial identity. However, numerous studies have demonstrated that African-Americans are less likely that Caucasians to be treated with opioid medications for pain (154, 155) despite evidence than African-Americans experience greater pain-related severity and disability compared to Caucasians (156). Concerted efforts will be made to recruit minority participants (especially African-Americans but also Latinos and other ethnic minorities) through Bellevue Hospital and the Manhattan VA, which have highly diverse and prevalent ethnic minority populations.

Inclusion of Children

Children under the age of 18 are excluded.

Data acquisition and transmission: *see section 11 source documents and access to source data*

Data entry methods: *see section 11 source documents and access to source data*

Data analysis plan: *see section 10 Statistical Considerations*

Quality assurance plan: *see section 12 Quality Assurance and Quality Control*

Reporting mechanisms of AEs/SAEs to the IRB, FDA, and NIDA: *see section 8 Assessment of Safety*

Reporting mechanisms of IRB actions to NIDA: *see section 8 Assessment of Safety*

Report of changes or amendments to the protocol: All significant changes to the protocol must be approved by the NIDA Program Officer prior to implementation.

Trial stopping rules: *See section 8.8 Study Halting Rules*

Conflict of interest: *See section 17 Conflict of Interest Policy*

Potential risks and benefits for participants: *see section 2.4 Potential Risks & Benefits*

Collection and reporting of AEs and SAEs: *see section 8 Assessment of Safety*

Management of SAEs or other study risks: *see section 8 Assessment of Safety*

Plans for Interim Analysis of efficacy data: *see section 10.4.7 Planned Interim Analysis*

Responsibility for data and safety monitoring

Medical and Safety Monitoring

The research team (project manager, coordinators, and research assistants) will submit any adverse events to the PI. The PI is responsible for reviewing all AEs and serious adverse events (SAEs) reported. All SAEs will be reviewed at the time they are reported in the electronic data capture system. All AEs will be reviewed on a weekly basis to observe trends or unusual events.

The PI will generate and present reports for Data Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs. A DSM Report will be submitted to NIDA annually.

Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be established, comprising at least three individuals appointed by the PI. The members of the DSMB will have any of the following backgrounds/expertise: pain, addiction, clinical trials expertise, biostatistics. This committee will be led by a chairperson and will meet (in person or by teleconference) prior to enrollment of the first participant, and at least annually thereafter, including meetings following completion of treatment of the first 5 completers, after completion of treatment of the first 10 completers, and upon completion of enrollment for the trial. Prior to each meeting, the PI will prepare a report to the Board including review of:

- Protocol and ICF changes
- Protocol violations and deviations
- Documentation of informed consent
- Enrollment and retention
- Investigator or key personnel changes
- Aggregate analysis of adverse events/serious adverse events
- Protection of confidentiality

Following each meeting, the board will provide the PI with a report including a recommendation to continue the study unchanged, continue with modifications of the protocol and/or the consent form to protect participant safety, or terminate the study.

DSMB Members
Kyle Kampman, MD (chair of DSMB)
Professor of Psychiatry
University of Pennsylvania Perelman School of Medicine
Center for Studies of Addiction
kampman@pennmedicine.upenn.edu

Joshua Lee, MD
Professor, Department of Population Health
Professor, Department of Medicine
NYU Grossman School of Medicine

Afrin Sagir, MD, MBBS
Assistant Professor of Anesthesiology and Critical Care
Penn Spine Center
Department of Anesthesiology and Critical Care
Hospital of the University of Pennsylvania
Perelman School of Medicine

Frequency of DSM reviews: *see section above- Responsibility for data and safety monitoring*

Content of DSM report DSM Board Plan: *see section above- Responsibility for data and safety monitoring*

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Site staff will be required to audit source documentation, including informed consent forms and HIPAA forms, regulatory documents and case report forms on a biannual basis. Site staff will be responsible for local quality assurance and will verify that study procedures are properly followed and that site staff are trained and able to conduct the protocol appropriately. If the site staff's review of study documentation indicates that additional training of study personnel is needed, this will be arranged as per the PI. Study team members will review each other's data for completeness, accuracy, and fidelity to the protocol.

10 Statistical Considerations

10.1 *Statistical and Analytical Plans (SAP)*

A formal SAP will be developed prior to un-blinding and database lock

10.2 *Statistical Hypotheses*

Hypothesis 1a (safety and tolerability): Compared to placebo, CBD will be well tolerated by participants with no treatment-related serious adverse events (SAEs) or persisting CBD-related AEs.

Hypothesis 1b (plasma opioid concentrations): Compared to placebo, CBD will not increase plasma opioid concentrations by greater than or equal to 150% at any of the assessment time-points post-randomization (1-day, 2-day, 1-week, and 2-weeks) relative to baseline.

Hypothesis 2 (pain measures: ***secondary efficacy outcome***): Compared to placebo, CBD will be associated with a greater reduction in pain measures relative to baseline.

Exploratory Aim 1: Compared to placebo, CBD will be associated with a greater reduction in anxiety relative to baseline.

Exploratory Aim 2: Compared to placebo, CBD will be associated with a greater improvement in depression relative to baseline.

Exploratory Aim 3: Compared to placebo, CBD will be associated with a greater improvement in insomnia relative to baseline.

Exploratory Aim 4: Compared to placebo, CBD will be associated with a greater reduction in opioid craving relative to baseline.

Exploratory Aim 5: Compared to placebo, CBD will be associated with a greater reduction in maintenance opioid dose relative to baseline.

10.3 *Analysis Datasets*

The following datasets will be analyzed:

- Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)
- The Modified Intention-to-Treat (m-ITT) population will contain all randomized patients who receive at least one dose of double-blind study medication and from whom at least one post-baseline efficacy measurement is obtained while on study medication.
- Safety Analysis Dataset: subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of investigational product)
- Evaluable or Per-Protocol Analysis Dataset: The evaluable subset of participants will be defined as having received daily study medication or placebo for a 2-week treatment period (through T4).

10.4 *Description of Statistical Methods*

10.4.1 General Approach

Regarding the continuous outcomes to be assessed, a Mixed Model for Repeated Measures (MMRM) statistical analysis will be performed to assess treatment effects of CBD relative to placebo. The model at each time point will include terms for treatment, time, and treatment by time interaction as factors and the baseline value for each score as a covariate. Parameter estimation will be based on restricted maximum likelihood (REML) and to begin an

unstructured covariate matrix. If the model fails to converge, the alternative form of the covariance matrix will be chosen based on Schwarz' Bayesian Criterion. Model-based LS means will be obtained for change from baseline to each time point for each treatment group. At each time point, contrasts between CBD and placebo will be obtained. The main focus of the statistical analysis will be to characterize the effect sizes and response rates across outcome domains. The modified intent to treat (m-ITT) population will contain all randomized patients who receive at least one dose of double-blind study medication and from whom at least one post-baseline efficacy measurement is obtained while on study medication. The efficacy analysis will be based on the m-ITT population as well as a per protocol analysis given the pilot nature of the trial. Two-sided hypothesis testing will be utilized. Tests with p-values less than or equal to 0.05 will be considered statistically significant, while those less than or equal to 0.10 will be considered suggestive. Since this trial is the first use of this type of treatment, no adjustments of p-values for multiple comparisons will be made. Thus, all control of type 1 error is contrast-wise. Mean treatment effect, Cohen's d, standard errors, and 95% confidence intervals will be derived from fully adjusted models on outcomes averaged across the treatment period.

10.4.2 Analysis of the Primary Endpoint(s)

For Hypothesis 1a (safety and tolerability), the incidence of AEs and SAEs will be summarized and tabulated for each group (CBD vs placebo) by system organ class, preferred term, severity, and likelihood of its relationship to the pharmacologic treatment. Between group differences in frequency of AEs and SAEs (T0-T4) will be analyzed using chi-squared tests.

For Hypothesis 1b (plasma opioid concentrations), the respective outcomes will be analyzed with an MMRM to assess between-group and within-group differences in change from baseline. The primary contrast is change from baseline to 2-day, and 1-week post-randomization/initiation of pharmacologic treatment with secondary analyses contrasting changes from baseline to 2-weeks post-randomization.

10.4.3 Analysis of the Secondary Endpoint(s)

For Hypothesis 2 (pain measures: ***secondary efficacy outcome***), the respective outcomes will be analyzed with an MMRM to assess between-group and within-group differences in change from baseline. The primary contrast is change from baseline to 1-week post-randomization/initiation of treatment with secondary analyses contrasting changes from baseline to final treatment visit at 2-weeks post-randomization.

10.4.4 Safety Analyses

See ***10.4.2 Analysis of the Primary Endpoint(s)*** section regarding Hypothesis 1a (safety and tolerability) and Hypothesis 1b (safety and plasma opioid concentrations).

AEs and SAEs, when present, will be collected on an AE Case Report Form at study visits. The form will include an assessment of clinical significance and study relatedness. Serious Adverse Events (SAEs) will be documented on an additional SAE form. Visual analog scales will be used to assess abuse potential.

The study may be stopped if there are untoward and concerning levels of AEs or SAE outcomes attributable to CBD or study participation. If the DSMB finds it is likely that CBD is contributing to negative outcomes, they will consider solutions including protocol changes or potentially stopping the study.

10.4.5 Adherence and Retention Analyses

The Study Drug Participant Self-administration Log will be used to assess medication adherence by recording daily self-administration of study medications. Plasma concentrations of CBD will also be collected at T1-T4 will be an additional assessment to verify treatment adherence.

Number of participants that complete the treatment phase of the study (through T4) and are lost to follow-up will be collected. Frequency of and reasons for discontinuation of the intervention or study follow-up will also be tallied.

10.4.6 Baseline Descriptive Statistics

Treatment groups will be compared on several baseline characteristics, including sex, age, race/ethnicity, education level, baseline measures of opioid maintenance medication [measured in morphine equivalent daily doses (MEDD)], opioid craving, pain measures (PCS, BPI), anxiety (PROMIS Anxiety), depression (PROMIS Depression), and sleep (PROMIS SRI). Categorical data will be tallied, and means and standard deviations of continuous scores will be calculated.

10.4.7 Planned Interim Analysis

10.4.7.1 Safety Review (*see section 8.9 Safety Oversight: DSMB*)

The DSMB will meet (in person or by teleconference) following completion of treatment of the first 5 completers, after completion of treatment of the first 10 completers, and upon completion of enrollment for the trial. Prior to each meeting, the PI will prepare a report to the Board including review of the aggregate analysis of adverse events/serious adverse events.

Following each meeting, the board will provide the PI with a report including a recommendation to continue the study unchanged, continue with modifications of the protocol and/or the consent form to protect participant safety, or terminate the study. The study may be stopped if there are untoward and concerning levels of AE or SAE outcomes attributable to CBD or study participation. If the DSMB finds it is likely that CBD is contributing to negative outcomes, they will consider solutions including protocol changes or potentially stopping the study.

10.4.7.2 Efficacy Review

There will be no interim efficacy analysis as part of this clinical trial.

10.4.8 Additional Sub-Group Analyses

None.

10.4.9 Multiple Comparison/Multiplicity

See ***10.4.1 General Approach*** section above.

10.4.10 Tabulation of Individual Response Data

Aside from AEs/SAEs, individual response data will not be presented.

10.4.11 Exploratory Analyses

For Hypothesis 3 (anxiety), Hypothesis 4 (depression), Hypothesis 5 (sleep), Hypothesis 6 (opioid craving), and Hypothesis 7 (opioid sparing), the respective outcomes will be analyzed with *t*-tests to assess changes from baseline.

10.5 *Sample Size/Power Calculation*

We will screen approximately 30 participants, and enroll approximately 20 participants to meet our recruitment goal (through week 2/T4). In this pilot study, the affordable sample sizes are obviously quite limited. Previously, Zheng et al. conducted a randomized controlled trial using electroacupuncture [real electroacupuncture (REA) versus sham electroacupunture (SEA)] as a therapeutic intervention to decrease opioid-like medication (OLM) dose in patients with chronic pain syndromes (33). Using a sample size of 35 (REA=17, SEA=18), at the end of the treatment period, reductions in OLM consumption in the REA versus SEA groups were 39% and 25%, respectively (p=0.056). With the sample size of 20 in this current proposal, we hope to identify comparable or stronger evidence of CBD in reducing pain (in hypothesis 2) and change in plasma opioid concentrations from baseline to specified time (e.g., 1-week) in hypothesis 1b, in patients with chronic radiculopathies maintained on COT. A two-sided *t*-test of mean differences at 2 weeks requires an effect size of .91 common standard deviation to have .80 power.

10.6 *Measures to Minimize Bias:* Blinding Integrity Assessments

10.6.1 Enrollment/Randomization/Masking Procedures

The trial will employ a double-blind pharmacologic intervention methodology where the investigational drug (CBD) and matched placebo oral softgel capsules will be masked in identically appearing capsules provided by the drug sponsor. Randomization will be performed at the completion of the Baseline visit, and as close as possible to the first drug administration at the T1 session in order to restrict the intent-to-treat sample to patients who actually receive study medication.

10.6.2 Evaluation of Success of Blinding

To evaluate the effectiveness of the blind, both participant and investigator treatment assignment guesses (i.e., whether participant received investigational drug vs placebo) will be collected at 2-weeks (T4).

10.6.3 Breaking the Study Blind/Participant Code

Breaking the blind will occur by PI judgment based on clinical safety considerations. Intentional and unintentional breaking of the blind will be reported to the appropriate regulatory entities (i.e., IRB, FDA, sponsor).

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a

single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

Data quality assurance (QA) includes all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirements(s) (ICH E6 1.46). Data quality control (QC) includes the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 1.47).

QC procedures will be implemented beginning with the data entry system, and data QC checks on the database will be generated. Any missing data or data anomalies will be identified for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 *Ethical Standard*

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 *Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 *Informed Consent Process*

13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

The following consent materials are submitted with this protocol:

- Telephone Pre-screening Form
- Key Information form
- Main Informed Consent Form
- Main Consent Comprehension Quiz

13.3.2 Consent Procedures and Documentation

An IRB-approved pre-screening form will be used to pre-screen individuals expressing interest in the study, to assess whether they are likely to qualify for the study. Interested patients who pass the pre-screening will be referred for informed consent. Pre-screening data will be immediately destroyed for patients who do not pass pre-screening or for patients who pass the pre-screening but decide not to enroll in the study.

Interested patients will be provided with an informed consent form including all pertinent details of the study including description of the following: the assessment interview and questionnaires; the follow-up interviews; description of experimental treatment; risks and benefits of study procedures; alternatives to participation in the study; confidentiality; emergency treatment and compensation for injury; payment for participation; a statement that patients will be informed of any new findings affecting the risks or benefits of the study; a statement that participation is voluntary and that the patient may withdraw at any time; and information about whom to contact with questions or in case of emergency. The consent form will also include assurances of confidentiality and a statement that participation is entirely voluntary, that the decision to participate will in no way influence other aspects of the patient's treatment, and that the participant is free to withdraw participation at any time. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A main ICF Comprehension Quiz will be included and an appropriately trained and delegated study staff member will administer the Comprehension Quiz to determine if sufficient comprehension of the study exists to proceed with study participation.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g., consent document presented orally) and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and study drug records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Health (NYULH). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYULH research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYULH.

Confidentiality of research material will be ensured by storing the research materials in locked cabinets. Material will be available only to project staff, and only as needed. All project staff will be thoroughly trained in issues relating to confidentiality. Participants will be identified in case report forms (CRFs) by initials and an identification code. Data will be entered into TrialMaster® programs designed specifically to protect patient privacy and confidentiality. Published reports will be based on group data; no individual data will be reported.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH/NIDA. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13.4.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to evaluate study eligibility and plasma concentrations of opioids and cannabinoids. No genetic testing will be performed.
- Samples will only be used for study-specific analyses and then destroyed. Samples will not be banked for future research.

13.5 Future Use of Stored Data

Data collected for this study will be stored in locked cabinets in NYULH Psychiatry Department space within the Ross Lab area in the psychiatry department at One Park Avenue. After the study is completed, the de-identified, archived data will be transmitted to and stored at GRM Document Management for use by other researchers including those outside of the study. Permission to transmit data to GRM Document Management will be included in the informed consent.

When the study is completed, access to study data will be provided through GRM Document Management.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection, interpretation, analysis, review, and reporting is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink will be used to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original. Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents will be consistent with the source documents or the discrepancies will be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into "Research Electronic Data Capture" using TrialMaster®, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated, or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor-investigator, if applicable.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations will be reported to the NYU SOM IRB and NIDA per their guidelines, respectively. The site PI/study staff is responsible for knowing and adhering to IRB requirements.

14.4 *Publication and Data Sharing Policy*

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and Pediatric Postmarket Surveillance studies
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA

15 Study Finances

15.1 *Funding Source*

This study is financed through a grant from the US National Institutes of Health (NIH)/National Institute on Drug Abuse (NIDA).

15.2 *Costs to the Participant*

Participants will not incur any costs as a result of participating in the study.

15.3 *Participant Reimbursements or Payments*

Participants will receive monetary compensation for research assessments as follows: Screen (S) = $50, Baseline (T0) = $25, 1-day assessment (T1) = $75, 2-day assessment (T2) = $75, 1-week assessment (T3) = $100, 2-week assessment (T4) = $75. Participants completing all of the assessments would therefore receive a total of $400.

16 Study Administration

16.1 Study Leadership

The study will be led by PI Stephen Ross and the core study team leadership will consist of the PI and the co-Is (Doan, Blessing, Cheatle).

Role for Dr Cheatle: As part of the review process with NIDA for this grant, NIDA stipulated that an NIH-funded pain and addiction clinical trialist be added as a study member. Dr Cheatle has this requested background and so was added as a sub-investigator as part of the grant and study. His roles will include assisting with: study design, use of optimal outcome measures, recruitment strategies, strategies for reduction in opioid maintenance dose, data analysis, and writing of manuscripts. Note that Dr Cheatle will not have access to participant identifiers and will not interact with research participants.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIDA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

20 Schedule of Events

Study Phase	Screen	Baseline	(Rx[1])	Rx	Rx	Rx
Study Visit	S1, 2, 3	B1	1	2	3	4
Target Weeks	-4 to -2	-2 to 0	1-day	2-day	1 (-2d)	2 (-2d)
Time		T0	T1	T2	T3	T4
Inclusion/Exclusion Criteria						
COVID-19 Screening	X	X	X	X	X	X
Screening Checklist	X					
Informed Consent (ICF)	X					
ICF Comprehension Quiz	X					
ICF Documentation	X					
Authorization for Release of Health Information	X					
Confidential Contact Information	X					
Demographics (Phen X Tier-1)	X					
Medical/Psychiatric History	X					
SCID 5	X					
Alcohol Test	X					
Physical Examination	X					
Clinical Labs	X				X[2]	X[2]
EKG	X					
Birth Control Documentation	X	X	X		X	X
Urine Pregnancy Test	X	X	X	X	X	X
Urine Drug Screen	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Eligibility (I/E) Checklist	X	X				
Randomization		**X**				
CBD/PCB Dispensed			X[3]	X[3]	X[3]	X[3]
Safety Assessments						
Vital Signs	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Suicidality (C-SSRS)	X	X	X	X	X	X
Sedation (RASS)			X	X	X	X
Field Sobriety Test			X	X	X	X
Pharmacokinetics						
CBD Plasma Levels			X[5]	X[4,5]	X[4,5]	X[4,5]
Opioid Plasma Levels		X	X[4]	X[4]	X[4]	X[4]
Opioid—Related Outcomes						
Opioid Maintenance Dose (MEDD)	X	X	X		X	X
Opioid Craving (VAS)		X	X	X	X	X
Secondary Efficacy Outcome: Pain Outcomes						
Brief Pain Inventory (BPI)		X	X	X	X	X
Pain Catastrophizing Scale (PCS)		X	X	X	X	X
Mental Health Outcomes						
Anxiety (PROMIS)		X	X	X	X	X
Depression (PROMIS)		X	X	X	X	X
Sleep (PROMIS)		X	X	X	X	X
Blinding Integrity						**X**
Self-Administration Medication Log	**X**	**X**	**X**	**X**	**X**	**X**
Participant Compensation	**X**	**X**	**X**	**X**	**X**	**X**

[1]Rx= Pharmacologic Treatment Period
[2]Liver function tests
[3]Study medication or placebo dispensed at visit for daily use until the next visit
[4]Blood drawn before starting CBD/PCB administration
[5]Blood draws after starting CBD/PCB administration