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
Document Type:	Informed Consent Form
Date of the Document:	• June 14, 2022

NYU Langone Health

Research Subject
Informed Consent Form

Title of Study:	A Phase I/II, Randomized, Double-Blind, Placebo-Controlled Trial of Cannabidiol for chronic radiculopathic pain syndromes maintained on chronic opioid therapy *s21-00230*
Principal Investigator:	Stephen Ross, MD Department of Psychiatry NYU School of Medicine 462 1st Avenue, A838 Email: Stephen.Ross@nyulangone.org Telephone: 212-263-6289
Emergency Contact:	Stephen Ross, MD Cell phone: (917) 848-7830

1. About volunteering for this research study

You are being invited to take part in a research study. Your participation is voluntary which means you can choose whether or not you want to take part in this study.

People who agree to take part in research studies are called “subjects” or “research subjects”. These words are used throughout this consent form. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. You may also decide to discuss this study and this form with your family, friends, or doctor. If you have any questions about the study or about this form, please ask us. If you decide to take part in this study, you must sign this form. We will give you a copy of this form signed by you for you to keep.

2. What is the purpose of this study?

The purpose of this research study is to see how safe and effective Cannabidiol (CBD) is for the treatment of chronic non-cancer spinal radiculopathic pain conditions in people maintained on an ongoing dose of opioid pain medications. We will assess the effects of CBD on opioid medication use, pain as well as aspects of thinking, emotions and behavior.

CBD is a drug found in the marijuana plant that does not appear to have addictive properties and is not known to be psychoactive (affect your mind). Even though the United States Food and Drug Administration (FDA) has approved CBD in the form of Epidiolex® for childhood seizure disorders, it has not approved CBD as a safe or effective treatment for chronic non-cancer radiculopathic pain conditions. Therefore, the use of CBD to treat opioid use and pain associated with chronic spinal non-cancer radiculopathy is considered experimental. Animal and human studies suggest that CBD may be helpful in treating opioid addiction and pain.

CBD works by activating receptors (proteins) in the brain known to effect a variety of processes such as immune function, appetite, pain sensation, mood, memory and the way you respond to stressful

situations. Even though CBD is found in the marijuana plant, it does not make people feel “high” the same way that marijuana does.

You will be randomly assigned (like a flip of a coin) to either CBD or a placebo group. You have a 50% (1 in 2) chance to be assigned to either group. Placebo means that you will receive capsules to take daily that will not have any CBD in them. You and your study doctor will not know whether you are taking CBD or placebo. In the event of an emergency, your study doctor can find out this information.

You are being asked to participate in this study because you want to decrease or stop your opioid analgesic maintenance dose but are not currently enrolled in another clinical trial assessing the effects of an anti-pain intervention.

3. How long will I be in the study? How many other people will be in the study?

Approximately 40 subjects will receive medication in this study at NYULMC. Up to 60 people will be consented in the study in order to reach the target of 40 subjects to receive medication. The total duration of participation in the study, including screening and follow-up visits, will be approximately 26 weeks. The total approximate time of contact during these 26 weeks is estimated at 40 hrs.

4. What will I be asked to do in the study?

If you agree to participate, the following will occur:

Screening Visit (4 hours)

If you agree to be in this study, the first visit will be the screening visits. The purpose of the screening visits is to make sure that you meet all of the conditions to participate in the study. The screening visits include medical and mental health evaluations, as well as assessments of your pain condition and opioid medication use. The medical evaluation must be done in-person at the study site, but you have the option to complete other portions of the screening visit at home, before you come to the study site to complete the medical evaluation.

Medical Evaluation (Approximately 1 hour)

You will have the following procedures done:

- Medical/Psychiatric history
- Demographics (age, race and ethnicity, gender, etc.)
- SCID-5 (Diagnostic Exam)
- Physical Exam
- Electrocardiogram (ECG or EKG), which measures the electrical activity of your heart
- Safety clinical laboratory measures: 10 cc of blood (about 2 teaspoons) will be drawn with a needle from a vein in your arm to check blood counts and the functioning of your liver and other organs (if you are a women of childbearing potential, we will also collect blood for a serum pregnancy test)
- Urine sample (approximately 1 tablespoon) will be collected for:
    - Urinalysis
    - To test for the presence of several drugs, including cocaine, methamphetamine, opiates, and marijuana. This test will be performed on site. You will be able to collect this urine in a

bathroom without anyone watching you. You will be informed of the results of the laboratory tests when they become available. Unless you are taking a medication for medical purposes, if you test positive for any of the drugs listed (including recreational or medical marijuana or any product containing CBD), you will not be allowed to participate in the study.
    - Women of child bearing potential will also have a urine pregnancy test done
- Vital signs (heart rate, blood pressure, and temperature)

- It is a requirement of the study that you are willing to allow for initial and ongoing communication between the study team and your treatment provider(s) prescribing chronic opioid therapy for chronic radicular pain condition. If it is necessary to determine your eligibility for the study, we may ask to see your personal information in records from hospitals, clinics, or doctor's offices where you may have received care in the past. We may also ask to speak with other clinicians who have treated you for medical and/or psychiatric conditions, but will not reveal the nature of the study without your permission.

- As part of 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 of your treatment providers prescribing opioids to you that they provide a naloxone prescription you. Naloxone is an opioid overdose antidote medication and will be used to manage risks related to opioid medication use.

You will receive a diagnostic interview assessing substance use and psychiatric disorders. This includes questions about symptoms of the most important mental illnesses, including use, abuse, and dependence on/of alcohol and drugs. We will also ask you in detail about your recent use of alcohol and drugs and about any current medications you are taking. We will also ask you about suicidal thoughts and behaviors and will monitor you for suicidal thoughts and behaviors throughout the trial at each study visit. If you qualify to participate in the study, you will be scheduled for a Baseline visit and 6 assessment visits over the next 24 weeks. Please refer to the Schedule of Assessments as follows:

In order to participate in this study, you will also need to identify at least two people who would know your whereabouts in case study personnel needed to find you during the study. The locator people may be told that we are calling from NYU, and may be given the name and phone number of study staff, but will not be given any other information about your participation without your permission. If we are unable to reach you with the information you have provided on the locator form, we may use publicly available data on the internet, like Facebook, in an effort to find updated contact information.

You will be given a Medication Self-Administration Log to record the prescription opioid medication(s) that you take. Between your Screening Visit and T1 Visit, this Medication Self-Administration Log will help us determine the precise time that your opioid medication is at its lowest level, which is crucial for determining when to take blood samples and schedule further visits. After the T1 Visit, you will also begin recording your doses of the study drug (CBD or placebo) on this log. You will be asked to bring the log to each of the remaining study visits. After the T8 visit (16-week), you will no longer be recording your use of study drug or your prescription opioid(s).

Baseline Visit (T0): Approximately 4 hours

At the baseline session (T0), prior to beginning the study treatment, you will be asked to complete a number of questionnaires and interviews, many of which will be repeated at later assessment sessions. These include questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating

harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana).

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

We will also need to collect a blood sample (1 or 2 tablespoons) to test for levels of prescription opioid analgesic plasma levels in your system. This sample will be sent to outside laboratories for testing, and will be accessible only to laboratory personnel. We will also collect several samples of blood to test for opioid and CBD levels over the course of the study: 3 samples at 1-day (T1), 3 samples at 2-day (T2), 3 samples at 1-week (T3), 3 samples at 2-weeks (T4), and 3 samples at 4-weeks (T6) after starting the medication intervention.

T1 (1-day) visit (beginning of study medication): Approximately 4 hours

At the T1 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana).

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

We will also need to collect 3 blood samples (1 or 2 tablespoons for each sample) over several hours at our NYU-HHC Clinical and Translational Science Institute (CTSI) at Bellevue Hospital to test for levels of prescription opioid analgesic plasma levels and CBD plasma levels in your system. To minimize the amount of needle sticks, we will place an initial intravenous catheter in one of your veins to collect the 3 blood samples. These samples will be sent to outside laboratories for testing, and will be accessible only to laboratory personnel.

Study Medication

At the T1 visit, you will receive your first dose of study medication (CBD or placebo) by mouth following a light meal. Specifically, you will receive 6 capsules of CBD (50mg per capsule) or the placebo. We will monitor you closely for a minimum of 3 hours to assess for safety. If there are no safety concerns following this initial administration during the T1 visit, we will give you instructions on how to use the study medication at home and will provide you with enough of the study medication to last until your next scheduled visit. You will be given medication to take home with you, and you will be instructed to take the medication each day. You will take 6 capsules in the morning (total dose of 300mg of CBD if you received CBD as study drug) and 6 capsules in the evening (approximately 12 hours apart), following a light meal, for the duration of 16 weeks. Sometimes we will ask you to bring your morning dose with you to a research visit to take in the laboratory. For the T2 visit, we ask that you bring in 6 capsules of your study medication to take in the morning at the NYU-HHC CTSI.

You will be instructed to start using your Medication Self-Administration Log to record all of the doses of the study drug (CBD or placebo) in addition to the prescription opioid medication(s) that you take, which you have been recording since the Screening Visit. You will be asked to bring this log to each of the

remaining study visits. After the T8 visit (16-week), you will no longer be recording your use of study drug or your prescription opioid(s).

T2 (2-day) visit: Approximately 4 hours

At the T2 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana).

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

We will also need to collect 3 blood samples (1 or 2 tablespoons for each sample) over several hours at our NYU-HHC Clinical and Translational Science Institute (CTSI) at Bellevue Hospital to test for levels of prescription opioid analgesic plasma levels and CBD plasma levels in your system. To minimize the amount of needle sticks, we will place an initial intravenous catheter in one of your veins to collect the 3 blood samples. These samples will be sent to outside laboratories for testing, and will be accessible only to laboratory personnel.

Study Medication

At the T2 visit, you will receive your morning dose of study medication (CBD or placebo) by mouth following a light meal. We will monitor you for a minimum of 3 hours to assess for safety. If there are no safety concerns following this initial administration during the T2 visit, we will give you instructions on how to use the study medication at home and will provide you with enough of the study medication to last until your next scheduled visit. You will be given medication to take home with you, and you will be instructed to take the medication each day. You will take 6 capsules in the morning (total dose of 300mg of CBD if you received CBD as study drug) and 6 capsules in the evening (approximately 12 hours apart), following a light meal, unless there was an adjustment (i.e., decrease) in your dose.

For the T3 visit, we ask that you bring in 6 capsules of your study medication to take in the morning at the NYU-HHC CTSI. You will also need to bring in your self-administration log.

T3 (1-week) visit: Approximately 4 hours

At the T3 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana).

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

We will also need to collect 3 blood samples (1 or 2 tablespoons for each sample) over several hours at our NYU-HHC Clinical and Translational Science Institute (CTSI) at Bellevue Hospital to test for levels of

prescription opioid analgesic plasma levels and CBD plasma levels in your system. To minimize the amount of needle sticks, we will place an initial intravenous catheter in one of your veins to collect the 3 blood samples. These samples will be sent to outside laboratories for testing, and will be accessible only to laboratory personnel.

Study Medication

At the T3 visit, you will receive your morning dose of study medication (CBD or placebo) by mouth following a light meal. We will monitor you for a minimum of 3 hours to assess for safety. If there are no safety concerns following this initial administration during the T3 visit, we will give you instructions on how to use the study medication at home and will provide you with enough of the study medication to last until your next scheduled visit. You will be given medication to take home with you, and you will be instructed to take the medication each day. You will take 6 capsules in the morning (total dose of 300mg of CBD if you received CBD as study drug) and 6 capsules in the evening (approximately 12 hours apart), following a light meal, unless there was an adjustment (i.e., decrease) in your dose.

For the T4 visit, we ask that you bring in 6 capsules of your study medication to take in the morning at the NYU-HHC CTSI. You will also need to bring in your self-administration log.

T4 (2 week) visit: Approximately 4 hours

At the T4 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana). We will also collect approximately 1 teaspoon of blood to assess your liver function. We will also ask you to guess whether you believe you are receiving the CBD or placebo.

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

We will also need to collect 3 blood samples (1 or 2 tablespoons for each sample) over several hours at our NYU-HHC Clinical and Translational Science Institute (CTSI) at Bellevue Hospital to test for levels of prescription opioid analgesic plasma levels and CBD plasma levels in your system. To minimize the amount of needle sticks, we will place an initial intravenous catheter in one of your veins to collect the 3 blood samples. These samples will be sent to outside laboratories for testing, and will be accessible only to laboratory personnel.

Study Medication

At the T4 visit, you will receive your morning dose of study medication (CBD or placebo) by mouth with food. We will monitor you for a minimum of 3 hours to assess for safety. If there are no safety concerns following this initial administration during the T4 visit, we will give you instructions on how to use the study medication at home and will provide you with enough of the study medication to last until your next scheduled visit. You will be given medication to take home with you, and you will be instructed to take the medication each day. You will take 6 capsules in the morning (total dose of 300mg of CBD if you received CBD as study drug) and 6 capsules in the evening (approximately 12 hours apart), following a light meal, unless there was an adjustment (i.e., decrease) in your dose.

For the T5 visit, we ask that you bring in 6 capsules of your study medication to take in the morning at the NYU-HHC CTSI. You will also need to bring in your self-administration log.

T5 (3 week) visit: Approximately 4 hours

At the T5 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana). We will also collect approximately 1 teaspoon of blood to assess your liver function. We will also ask you to guess whether you believe you are receiving the CBD or placebo.

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

Study Medication

At the T5 visit, you will receive your morning dose of study medication (CBD or placebo) by mouth with food. We will monitor you for a minimum of 3 hours to assess for safety. If there are no safety concerns following this initial administration during the T5 visit, we will give you instructions on how to use the study medication at home and will provide you with enough of the study medication to last until your next scheduled visit. You will be given medication to take home with you, and you will be instructed to take the medication each day. You will take 6 capsules in the morning (total dose of 300mg of CBD if you received CBD as study drug) and 6 capsules in the evening (approximately 12 hours apart), following a light meal, unless there was an adjustment (i.e., decrease) in your dose.

For the T6 visit, we ask that you bring in 6 capsules of your study medication to take in the morning at the NYU-HHC CTSI. You will also need to bring in your self-administration log.

T6 (4-week) visit: Approximately 4 hours

At the T6 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana). We will also ask you to guess whether you believe you are receiving the CBD or placebo.

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

We will also need to collect 3 blood samples (1 or 2 tablespoons for each sample) over several hours at our NYU-HHC Clinical and Translational Science Institute (CTSI) at Bellevue Hospital to test for levels of prescription opioid analgesic plasma levels and CBD plasma levels in your system. We will also collect approximately 1 teaspoon of blood to assess your liver function. To minimize the amount of needle sticks, we will place an initial intravenous catheter in one of your veins to collect the 3 blood samples.

These samples will be sent to outside laboratories for testing, and will be accessible only to laboratory personnel.

Study Medication

At the T6 visit, you will receive your morning dose of study medication (CBD or placebo) by mouth following a light meal. We will monitor you for a minimum of 3 hours to assess for safety. If there are no safety concerns following this initial administration during the T6 visit, we will give you instructions on how to use the study medication at home and will provide you with enough of the study medication to last until your next scheduled visit. You will be given medication to take home with you, and you will be instructed to take the medication each day. You will take 6 capsules in the morning (total dose of 300mg of CBD if you received CBD as study drug) and 6 capsules in the evening (approximately 12 hours apart), following a light meal, unless there was an adjustment (i.e., decrease) in your dose.

For the T7 visit, we ask that you bring in 6 capsules of your study medication to take in the morning at the NYU-HHC CTSI. You will also need to bring in your self-administration log.

T7 (8 week) visit: Approximately 2 hours

At the T7 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana). We will also collect approximately 1 teaspoon of blood to assess your liver function.

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

Study Medication

At the T7 visit, we will provide you with enough of the study medication to last until your next scheduled visit. You will be given medication to take home with you, and you will be instructed to take the medication each day. You will take 6 capsules in the morning (total dose of 300mg of CBD if you received CBD as study drug) and 6 capsules in the evening (approximately 12 hours apart), following a light meal, unless there was an adjustment (i.e., decrease) in your dose. This will be the final medication administration and there will not be an option to receive any further study medication.

You will also need to bring in your self-administration log for the last time and will not need to continue to record your daily use of prescription opioid(s) or study medications.

T8 (16 week) visit: Approximately 4 hours

At the T8 visit, you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also check your vital signs (heart rate, blood pressure, and temperature) and collect a urine sample (approximately 1 tablespoon) to test for the presence of several drugs (including cocaine, opioids, methamphetamines and marijuana). We will also collect approximately 1 teaspoon of blood to assess

your liver function. We will also ask you to guess whether you believe you are receiving the CBD or placebo.

If you are a woman of childbearing potential we will also perform a urine pregnancy test to minimize the risk of undetected pregnancy while you are in the study.

Study Medication
You will not receive any further study medication for the remainder of the trial until the final study visit T9 (24-weeks).

T9 (24 week) visit: Approximately 2 hours (may be conducted remotely)

At the T9 visit (final study visit), you will be asked to complete questionnaires about any recent medication, drug and alcohol use (since the last visit), problems you may have experienced related to opioids, your motivation and confidence to reduce your analgesic opioid dose, your craving for opioids, your degree of pain, any thoughts or actions indicating harm to yourself or others and your current mood and sleep patterns. We will also collect approximately 1 teaspoon of blood to assess your liver function.

Potential for dose adjustments or cessation of study medication

If you are experiencing potential negative side effects from the study medication, it is possible to have your study medication adjusted by the study physician. The medication administration may be discontinued by the study physician if it is deemed that continued administration of the medication would post a significant medical risk.

Information about blood samples collected for opioid and CBD analyses

Any personal information that could identify you will be removed from the blood sample specimens. The blood samples will be shipped to the University of Buffalo where the pharmacokinetic analyses (measuring opioid analgesic plasma levels and CBD plasma levels) will take place.

Any identifiable specimen collected and/or used for the purposes of this research will not be used or distributed for future research studies.

Identifiers will be removed from the identifiable private information. After such removal, the information may be used for future research studies or shared with other researchers and we will not request additional informed consent from you to use these specimens or information as we have noted here.

Study Phase	Screen	Baseline	(Rx[1])	Rx	Rx	Rx	Rx	Rx	Rx	Rx	F/U
Study Visit	S1, 2, 3	B1	1	2	3	4	5	6	7	8	9
Target Weeks	-4 to -2	-2 to 0	1-day	2-day	1 (-2d)	2 (-2d)	3 (-2d)	4 (-2d)	8 (-4d)	16 (-4d)	24 (-4d)
Time		T0	T1	T2	T3	T4	T5	T6	T7	T8	T9
Inclusion/Exclusion Criteria											
COVID-19 Screening	X	X	X	X	X	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										
Physical Examination	X										
Clinical Labs	X							X[2]	X[2]	X[2]	X[2]
EKG	X										
Birth Control Documentation	X	X				X		X	X	X	X
Urine Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Eligibility (I/E) Checklist	X	X									
Randomization		**X**									
CBD/PBO dispensed			X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]		
Safety Assessments											
Vital Signs	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X
Suicidality (CSSRS)	X	X	X	X	X	X	X	X	X	X	X
Sedation (RASS)			X	X	X	X	X	X			
Field Sobriety Tests			X	X	X	X	X	X			
Pharmacokinetics											
CBD Plasma Levels			X[4]	X[4,5]	X[4,5]	X[4,5]		X[4,5]			
Opioid Trough Plasma Levels		X	X[5]	X[4]	X[4]	X[4]		X[4]			
Opioid—Related Outcomes											
Primary Efficacy Outcome: Opioid Dose (MEDD)	X	X			X			X	X	X	X
Motivation: Change Opioid Use		X			X			X	X	X	X
Opioid Misuse (COMM)		X			X			X	X	X	X
Opioid Craving (VAS)		X			X			X	X	X	X
Opioid Withdrawal (SOWS)		X			X			X	X	X	X
Pain Outcomes											
Brief Pain Inventory (BPI)		X			X			X	X	X	X
Pain Catastrophizing Scale (PCS)		X			X			X	X	X	X
Quality of Life (PROMIS)		**X**								**X**	**X**
Mental Health Outcomes											
Anxiety (PROMIS)		X			X			X	X	X	X
Depression (PROMIS)		X			X			X	X	X	X
Sleep (PROMIS)		X			X			X	X	X	X
Blinding Integrity								**X**		**X**	
Self-Administration Medication Log	**X**	**X**	**X**	**X**	**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

5. What are the possible risks or discomforts?

Risk of Study Drug

The available evidence suggests that CBD is safe and well-tolerated in human subjects. 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. 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.

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. The most common AEs in all the trial arms were diarrhea, nausea, headache, and tiredness. Diarrhea and headache were more common in subjects taking CBD compared with placebo.

The recommended dose of the FDA-approved Epidiolex® (oral CBD administered mostly to children to treat seizure disorders, Dravet Syndrome and Lennox-Gastaut) 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% or at least 10 out of every 100 patients) and greater than placebo) were

- Sleepiness
- Decreased appetite
- Diarrhea
- Decreased energy
- Rash
- Difficulty sleeping
- Infections
- Increase in liver enzymes: CBD (in the form of Epidiolex™) has been reported to be associated with dose-related elevations in liver transaminases (ALT and/or AST). There also was a clear dose association: 8% (8 out of 100) elevations overall in the 10 mg/kg group and 16% (16 out of 100) in the 20 mg/kg group. 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. Identified risk factors for transaminase elevation included taking other medications such with valproic acid (a medication used to treat seizure disorders, mood conditions and migraine headaches), and elevated baseline liver function tests. 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
    - We will assess your liver function at screening as well as at 4- weeks, 8-weeks, 16-weeks, and 24-weeks after starting study medication.

There is a theoretical risk that CBD may raise your prescription opioid levels, especially during the first month of receiving CBD, if you end up in the group receiving CBD. Increased opioid levels can potentially be dangerous and could result in an opioid overdose and death. To minimize this risk, we will closely

monitor you, especially during the first month after starting study medication since this represents the greater risk period from the perspective of increased opioid levels. We will specifically protect you from potential increased opioid levels in the study by the following:

- We will educate you on the signs and symptoms that may indicate increased opioid levels. These typically include feeling lethargic, slowed breathing, and small pupil size. We will provide with a contact number to reach study personnel in between the weekly visits for the first month of receiving study medication.
    - You will be able to reach the principal investigator Dr. Stephen Ross at any time by calling 917-848-7830

- Regarding visits T1-T6, you will be administered the first daily morning dose of medication (CBD 300mg or placebo) for that treatment period and will be evaluated for a minimum of 3 hours at a supervised clinical laboratory setting within the Ross Lab area at Bellevue Hospital (i.e., A8) or the NYU-HHC Clinical & Translational Science Institute (NYU-HHC CTSI) at Bellevue Hospital. You 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 assessing your breathing and oxygenation status). If you develop clinical signs and symptoms suggestive of opioid intoxication or overdose (i.e., respiratory suppression (breathing poorly), decreased oxygenation, lethargy (tiredness/lack of energy)), you will be immediately evaluated clinically and appropriate medical steps will be taken to assure your safety (i.e., Narcan/naloxone administration, oxygen administration, inpatient hospitalization, breaking the blind (your doctor will confirm whether you were taking CBD or placebo), discontinuing study medication).
    - You will not be permitted to leave the study site for visits T1-T6 until you are able to pass a standard field sobriety test.

- As part of 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 treatment providers, who are prescribing prescription opioids to you, that they provide a naloxone prescription for you. Naloxone is an opioid blocking medication that is used as an antidote (or to cancel the effects of opioids) to treat opioid overdoses. The study team will train you on the use of naloxone. In the case of an opioid overdose, naloxone would be administered to you by a family member, spouse/partner, friend or healthcare provider. It would be important that whoever is in close contact with you (i.e. living with you, sees you regularly) is trained in how to administer naloxone if necessary.

The CBD and placebo medications for this study are provided by ANANDA Scientific. Note that the specific drug product to be used in this trial has only been studied in healthy volunteers (and at lower doses than will be used in this trial) and has not been administered to patients previously. Also, note that this drug products is not Epidiolex™ (the marketed and approved CBD drug product) and is an experimental drug product. In a human safety study conducted on the formulation of CBD (A1002N5S) that will be used in this study, 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.

Since it is possible that there is a theoretical risk of adverse drug interactions between CBD and grapefruit (in terms of grapefruit potentially increasing levels of CBD when the two are taken together), you are to avoid consuming grapefruit or grapefruit juice during the duration of the study.

There is a chance you will not actually be taking medicine that will treat your condition. In this case, your condition might not improve or could get worse. You could miss the benefits or harms (if any) of the study medication.

It is possible that there are unforeseeable risks associated with the study medication or other aspects of participation in the trial.

Other Risks

Blood Drawing Risks

Drawing blood may cause temporary pain and discomforts from the needle stick, occasional bruising, sweating, feeling faint or lightheaded, and in rare cases infection.

Risks of Assessment Procedures

There are no known psychological risks associated with the questionnaires used in the study, most of which have been used extensively in clinical populations. It is possible that discussion of substance use and psychiatric symptoms may cause you some emotional discomfort or temporary stress. One of the investigators of the project will be available to meet with you if you become distressed about any aspect of the study and wish to discuss it.

Risks to Confidentiality and Potential Legal Consequences

Information from this study may be submitted to the U.S. Food and Drug Administration (FDA). Medical records that identify you and the consent form you signed may be inspected by the FDA and the New York University School of Medicine's Institutional Review Board (the Human Research Protections Office). 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, your identity will not be disclosed in those presentations.

For more information about risks and side effects, ask a study investigator.

6. Can I be in the study if I am pregnant or breastfeeding?

Because taking part in this study may harm an embryo, fetus, or breastfeeding baby, you should not become pregnant, breastfeed a baby, or father a child while participating in this study. Other risks may not yet be known.

If you are currently pregnant, you will not be able participate in the study. You should not become pregnant while you are participating in this study. If you are able to become pregnant, you will be required to use a medically accepted method of birth control while you participate in the study:

- Hormonal methods like birth control capsules, patches, vaginal rings or implants,
- Barrier methods such as condoms or a diaphragm used with spermicide (a foam, cream or gel that kills sperm),
- Intrauterine device (IUD),
- Abstinence (no sex).

If you become or you think you have become pregnant during the study, you must tell the principal investigator right away and must tell your obstetrician or other health care provider caring for you during

your pregnancy that you took part in this study. If you become pregnant, you will have to stop taking part in the study for safety reasons. The principal investigator may ask you to provide information about the outcome of your pregnancy and the health of your baby.

Note to Men

Because the effects of participating in this study on sperm are unknown, you will be required to use a medically accepted method of birth control while you participate in the study using one of the methods described above.

7. What if new information becomes available?

During the course of this study we may find more information that could be important to you. This includes information that might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

8. What are the possible benefits of the study?

There may or may not be benefits to you from participating in this study. It is possible that some study subjects who receive CBD may experience a reduction in their opioid pain medication use and pain during the study. However, if you receive such benefit, because CBD is not FDA-approved for treating opioid use or pain in chronic spinal non-cancer radiculopathy, your doctor cannot prescribe it after you finish the study. Also, you may not get any benefit from being in this research study. Knowledge gained through this study may aid the development of more effective treatments for individuals with chronic non-cancer radiculopathy pain who are on opioid pain medications.

9. What other choices do I have if I do not participate?

Standard of care for outpatient treatment of chronic radiculopathic pain consists of a variety of treatments including medications, physical therapy/rehabilitation, psychological (i.e., cognitive-behavioral therapy, mindfulness-based interventions), interventional (i.e., nerve blocks, neurostimulators, joint injections), and other (i.e., acupuncture, massage, chiropractic) modalities. These alternatives may be discussed with your personal physician.

10. Will I be paid for being in this study?

In return for your time and the inconvenience of participating in this study, you will be compensated for the study visits you complete.

Subjects will receive monetary compensation for research assessments as follows:

Study Visit	Amount
Screen (S)	$20
Baseline (T0)	$60
1-week assessment (T3)	$40
4-week assessment (T6)	$40
16-week (T8)	$40
24-week (T9)	$40

If you do not complete all of the visits, you will be paid for each of the visits you complete. If you complete all study visits, you will be compensated a total of $240.

As is required by the laws that apply to NYU Langone, in order for you to receive a payment (i.e., check, Clincard, or bank gift card), you need to give the study staff either your Social Security number or your Alien Registration number and will be asked to complete a IRS W9. If you do not have either of these numbers or are not willing to complete the IRS, you may be in the study but will not receive any payment.

You are required to track all payments made to you by NYU Langone for your participation in any research for this calendar year. You must let us know immediately if/when the total research payments presently equal or is likely to exceed $600.00 total (not including travel reimbursements) for this calendar year. If your total payments (for one or more studies) reach $600.00, please advise the study principal investigator, Stephen Ross, MD who can be contacted at: 917-848-7830 or Stephen.Ross@nyulangone.org.

In order to receive payments for your participation in research, you may need to provide your Social Security number. This is because NYU Langone is required to report to the Internal Revenue Service (IRS) any amounts that are paid to research participants that are equal to or greater than $600.00, and you may be taxed on these research payments above $600.00. If you will receive payments in any amount by a check, you will need to provide your Social Security number or Alien Registration number and will be asked to complete an IRS W9. If you do not have either of these numbers or are not willing to complete the IRS, you may be in the study but will not receive any payment.

11. Will I have to pay for anything?

You will not be billed for the cost of tests and procedures directly associated with this study.

You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs or you do not have insurance, these costs will be your responsibility.

12. What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

For medical emergencies contact 911. If you think you have been injured as a result of taking part in this research study, tell the principal investigator as soon as possible. The principal investigator's name and phone number are listed at the top of page 1 of this consent form.

There are no plans for the NYU School of Medicine or Medical Center to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

13. When is the study over? Can I leave the Study before it ends?

This study is expected to end after all subjects have completed all visits, and all information has been collected. This study may also be stopped or your participation ended at any time by your physician, the study sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The principal investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The study sponsor, the principal investigator, the Food and Drug Administration (FDA) or other body responsible for monitoring the safety of the study has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Leaving the study will not interfere with your future care, payment for your health care or your eligibility for health care benefits.

14. How will you protect my confidentiality?

Your medical information is protected health information, or "PHI", and is protected by federal and state laws, such as the Health Insurance Portability and Accountability Act, or HIPAA. This includes information in your research record as well as information in your medical record at NYU Langone Health. In compliance with NYU Langone Health policies and procedures and with HIPAA, only those individuals with a job purpose can access this information.

Medical information created by this research study may become part of your medical record. We may include your research information in your medical record for several reasons, including for the billing of services provided in connection with the study, to securely document any medical services you receive, and so that other members of the NYU Langone Health community who may treat you have access to important information about your health.

You have a right to access information in your medical record. In some cases, when necessary to protect the integrity of the research, you will not be allowed to see or copy certain information relating to the study while the study is in progress, but you will have the right to see and copy the information once the study is over in accordance with NYU Langone Health policies and applicable law.

Certificate of Confidentiality

To help us further protect your confidentiality, this research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The NIH has issued a Certificate of Confidentiality for this research. This adds special protection for the research information (data, documents, or biospecimens) that may identify you.

Research information protected by this Certificate of Confidentiality cannot be disclosed to anyone else who is not connected with the research, without your consent. With this Certificate of Confidentiality, the researchers may not disclose or use research information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, without your consent. However, disclosure, without your consent, is still necessary if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases).

The Certificate of Confidentiality cannot be used to refuse a request for information from appropriate government agencies responsible for project oversight.

The Certificate of Confidentiality does not prevent you from releasing information about yourself and your involvement in this research, including for your medical treatment. Federal regulations may also allow for the use or sharing of information for other scientific research.

By agreeing to be in this research and signing below, you are giving your consent to share research information with others at NYU Langone Health. This means that your research information, including lab results and information about the investigational drug used in this study, may be included in your NYU Langone Health electronic medical record.

15. HIPAA Authorization

As noted in the Confidentiality section above, federal law requires us, and our affiliated researchers, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions. We are asking for your permission (authorization) to use and share your health information with others in connection with this study- in other words, for purposes of this research, including conducting and overseeing the study.

Your treatment outside of this study, payment for your health care, and your health care benefits will not be affected even if you do not authorize the use and disclosure of your information for this study.

What information may be used or shared with others in connection with this study?

All information in your research record for this study may be used and shared with those individuals listed in this section. Additionally, information in your medical record that the research team believes may be important to the study may be accessed by those listed here. This includes, for example, results from your physical examinations, laboratory tests, procedures, questionnaires, and diaries.

Who may use and share information in connection with this study?

The following individuals may use, share, or receive your information for this research study:

- The research team, including the Principal Investigator, study coordinators, and personnel responsible for the support or oversight of the study
- The study sponsor: The National Institute on Drug Abuse (NIDA)/The National Institutes of Health (NIH)
- Governmental agencies responsible for research oversight (e.g., the Food and Drug Administration or FDA).
- Health care providers, including your doctors and others who provide services to you in connection with this study, and laboratories or other individuals who analyze your health information in connection with this study.
- The Data & Safety Monitoring Board (DSMB)
- The data team: DataCore at New York University Langone to manage and maintain integrity of study data
- University of Buffalo (under the direction of Gene Morse) who will be conducting the pharmacokinetic analyses of the opioid and CBD plasma collections
- GRM Document Management to save and store study data once the study has been completed

Your information may be re-disclosed or used for other purposes if the person who receives your information is not required by law to protect the privacy of the information.

What if I do not want to give permission to use and share my information for this study?

Signing this form is voluntary. You do not have to give us permission to use and share your information, but if you do not, you will not be able to participate in this study.

Can I change my mind and withdraw permission to use or share my information?

Yes, you may withdraw or take back your permission to use and share your health information at any time for this research study. If you withdraw your permission, we will not be able to take back information that has already been used or shared with others. To withdraw your permission, send a written notice to the principal investigator for the study noted at the top of page 1 of this form. If you withdraw your permission, you will not be able to stay in this study.

How long may my information be used or shared?

Your permission to use or share your personal health information for this study will never expire unless you withdraw it.

16. Electronic Medical Record and Release of Study Related Information

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of your medical chart within NYU Langone Health. An EMR is simply a computer version of a paper medical record.

If you are or have been a patient at NYU Langone Health in the past, you have an EMR at NYU Langone Health. Information from your research participation will be added to this EMR.

If you have never been a patient at NYU Langone Health, you may not have an EMR at NYU Langone Health. In connection with your participation in this study, an EMR will be created for you. The purpose of your EMR at NYU Langone Health will be to facilitate this research study and allow the researchers to maintain information arising from your participation in this research study. The creation of this EMR is a requirement of your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility, for example, your name, the name of your primary doctor, the type of insurance you have, your date of birth and other health-related information.

What may be placed in the EMR?

Information related to your participation in the research (e.g., laboratory tests, research-related notes, imaging studies, and clinical procedures, etc.) will be placed in your EMR maintained by NYU Langone Health.

This information will be accessible to other members of the NYU Langone workforce that are not part of the research team. Information within your EMR may also be shared with others who NYU Langone Health has determined may appropriately have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Will I have access to research-related information within the Electronic Medical Record?

The 21st Century Cures Act allows patients increased access to their EMR. If you agree to participate in this study, this means that any research-related information placed in your EMR will be available to you immediately.

As a research participant, this means that you have immediate access to any research-related information that is placed in your EMR before the researchers have had an opportunity to review the information.

In this study, some research-related information in your EMR will not be available to you until the end of the study. This information will not be accessible in your EMR immediately in order to protect the integrity of the research trial results.

Results in the medical record that will not be immediately accessible:

- *Results of the blood testing that is being done, including tests of blood counts, opioid and CBD levels, and pregnancy.*

The researchers will provide you access to this research-related information in your EMR when the study is over.

17. Optional permission for future use

NYULMC would also like to store, use, and share your health information from this study in research databases or registries for future research conducted by NYULMC or its research partners. To give this additional permission, check the box below and write your initials where indicated. You may still participate in this study even if you do not give us this additional permission.

NYULMC will continue to protect the confidentiality and privacy of this information as required by law and our institutional polices. If you give this additional permission, you will continue to have the rights described in this form. You have the right to take back this additional permission at any time.

☐ **I agree** to allow the study team to store, use, and share my health information from this study in research databases or registries for future research conducted by NYULMC or its research partners.

☐ I **do not** want the study team to store, use, or share my health information from this study in research databases or registries for future research conducted by NYULMC or its research partners.

_____ _____
Signature of Subject _____ Date _____

18. The Institutional Review Board (IRB) and how it protects you

The IRB reviews all human research studies – including this study. The IRB follows Federal Government rules and guidelines designed to protect the rights and welfare of the people taking part in the research studies. The IRB also reviews research to make sure the risks for all studies are as small as possible. The NYU IRB Office number is (212) 263-4110. The NYU School of Medicine's IRB is made up of:

- Doctors, nurses, non-scientists, and people from the Community

19. Who can I call with questions, or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on top of the page 1 of this consent form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Institutional Review Board (IRB) at (212) 263-4110.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website site at any time.

When you sign this form, you are agreeing to take part in this research study as described to you. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer.

Name of Subject (Print)	Signature of Subject	Date
Name of Person Obtaining Consent (Print)	Signature of Person Obtaining Consent	Date