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June 20, 2025

Re: NCT05076370

Attached please find the most recent informed consent form for the study, “Safety and Tolerability of Cannabidiol Among Persons with Opioid Use Disorder Receiving Methadone or Buprenorphine” (PI: De Aquino; NCT05076370).

The goal of the study is to examine the safety, tolerability, and efficacy of oral cannabidiol (Epidiolex) as an adjunctive treatment for persons with comorbid opioid use disorder and chronic pain who receive opioid agonist maintenance treatment.

This human laboratory crossover study will include a total of 40 participants across two consecutive phases: One open-label phase including 6 participants (NCT05076370), and one placebo-controlled phase including 34 participants (NCT04587791). We obtained initial approval for the open-label study on 07/02/2020, and continuing reapproval for the placebo-controlled phase on 04/17/2025.

In the open-label phase, we administered single doses of 400 mg, 800 mg, and 1200 mg of CBD, across 3 test sessions, using a dose-escalation paradigm. The open-label phase will ensure the collection of critical safety data and inform the subsequent placebo-controlled phase. The placebo-controlled phase will administer placebo, 400 mg, 800 mg, and 1200 mg of CBD, across 4 test sessions, in a random order. This study is conducted at the VA Connecticut Healthcare System and at Yale University and has been approved by the Institutional Review Board of both institutions (VA Connecticut Healthcare Human Subjects Subcommittee and Yale University Human Investigation Committee).

Attached please find the up-to-date study informed consent form. If you have any questions, please do not hesitate to contact me at 203- 923-5711 Ext. 12916 or at the email address provided in this letter.

Sincerely,

Joao P. De Aquino, M.D.

Subject Name_____ Date:_____

Title of Study: Cannabidiol Pharmacotherapy for Comorbid Opioid Use Disorder and Chronic Pain (Pilot Safety Phase)

Principal Investigator: Joao P. De Aquino, M.D.. Version Date: 8/11/2021

RESEARCH SUMMARY

WHAT IS THE STUDY ABOUT AND WHY ARE WE DOING IT?

We are asking you to if you choose to volunteer for a study using a medication called Cannabidiol (CBD). We will look into whether this medication is safe for people with opioid use disorder and chronic pain who are receiving treatment with opioids. This summary is to give you information to help you decide if you wish to participate. We have included detailed information after this brief summary. Please feel free to contact the research team with any questions. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

In this study, you will be asked to attend an initial evaluation visit and three test sessions. During the test sessions, you will be asked to take medication containing doses of CBD. The doses of CBD will be a little higher each day (400 mg, 800 mg, 1200 mg). You will also be asked to complete paper and computer questionnaires. A research team that includes a study physician and a study nurse will monitor you for any side effects from CBD, like sleepiness.

By doing this study, we hope to learn how CBD affects people with opioid use disorder and chronic pain. We also want to see if CBD can be safely given with opioids, like buprenorphine or methadone. Your participation will last about 7-8 hours per day, for three test sessions. Each test session will be separated by at least 72 hours.

The purpose of this study is to gather information if CBD can be used as a potential treatment. CBD is the second most common ingredient of marijuana, after delta-9-tetrahydrocannabinol (THC). CBD (“Epidiolex”) is also a medication approved by the FDA to treat epilepsy in children.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You might choose to volunteer for this study to contribute to medical science, even though you may not personally benefit from it. It is important to emphasize that CBD is not an FDA-approved treatment for opioid use disorder or chronic pain. For a complete description of benefits, see the Research Details.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

You may choose not to volunteer for the study because it involves the taking a medication, having your blood drawn, or providing personal information. For a complete description of risks, see the Research Details.

This is not a treatment study, so there are no alternative treatments or procedures offered instead of participation. Since your participation in this study is voluntary, the alternative would be not to participate.

DO YOU HAVE TO TAKE PART IN THE STUDY?

You will not lose any services, benefits, or rights if you choose not to volunteer. If you decide to take part in the study, it should be because you really want to volunteer.

RESEARCH DETAILS

WHAT IS THE PURPOSE OF THIS STUDY?

The ultimate goal of this research is to learn how to better treat opioid use disorder and chronic pain. As a first step, we will test if CBD can be safely administered with methadone and buprenorphine. The knowledge gained with this study will help us to do future studies using CBD for opioid use disorder and chronic pain.

HOW LONG WILL I BE IN THE STUDY?

We plan to include six men and women with opioid use disorder either on methadone (three participants) or buprenorphine (three participants) in this research study.

This research study is expected to take approximately 6 months. Your individual participation in the project will take place over a period of approximately 3 weeks. One initial evaluation visit and three tests visits; each test visit separated by at least 72 hours.

WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

If you decide to participate in the research study, the following procedures will be followed:

Screening Session*:* First, a member of the research team will go over the consent form you are currently reading. Second, a physician will interview you and give you a physical examination. You will be asked detailed questions about your past hospitalizations, medical problems, and treatments you have received. We will also ask about your mental health and drug use history. Third, we will order some tests: an electrocardiogram (to examine the health of your heart; and routine blood and urine screening tests, to help decide if it's safe for you to participate. If your urine is positive for drugs of abuse (for example: cocaine, heroin and benzodiazepines) or if you are pregnant, you will not be allowed to participate in the study. The screening will last about 2 hours and it may take one week before we receive the test results. You will not be charged for these tests, and you will not be paid for completing them. If you request, the results of these tests will be made available to you, or to your medical doctor.

Based on the test results, we will let you know if you are able to participate in the study. After the screening session, this study will have 3 test sessions, each separated by 3 days. The test sessions will last for approximately 7-8 hours.

Test Session: First, you will have a small IV catheter placed into a vain in one of your arms by the Biostudies nursing staff. In the event that catheter placements can't be obtained, the test day will be rescheduled.

During the three test sessions, you will receive doses of CBD that are a little higher each day: 1) CBD 400 mg, 2) CBD 800 mg, 3) CBD 1200 mg. In the first test session, you will receive CBD at 400 mg, the second session 800 mg, and the third session 1,200 mg CBD. You will only receive a higher dose of CBD if the research team finds that you do well on the lower dose, by not feeling sedated or sleepy. CBD will be given always by mouth, in a liquid form.

Blood will be drawn on three occasions during the test sessions using an IV line. There are usually no serious medical problems with blood drawing, but pain, bruising, or infection may occur. CBD has also been given along with low doses of opioids, but not methadone or buprenorphine. All of the doses used are within the dose range approved by the FDA to treat rare forms of seizures in children.

During each of the three test sessions of the study, you will come to Building 36 located at the VA Connecticut Healthcare System. These test days will start at around 8 AM and will last approximately 7-8 hours. Since we will provide you with a light snack before each test session and a small meal at the end of each test session, we ask you not to eat after midnight prior to your test sessions. You can drink your usual amount of coffee or other caffeinated beverages 2 hours *before* the test sessions. You will be asked not to drink caffeinated beverages *during* the test sessions.

The first thing we will do when you arrive is to take measurements of your heart rate, blood pressure, mood, and memory. Then, we will give you a dose of the study medication (CBD 400 mg, 800 mg, 1200 mg).

Starting half an hour after receiving the study medication, we will take repeated measurements of your heart rate, blood pressure, mood, memory and attention. We will also take measurement of your sensitivity to pain. We will also measure your reaction and attention to images or words that may remind you about opioids or pain. Before discharge at the end of each test session, you will be evaluated by a physician. You will only be discharged once you are back to your usual self with regards to your psychological, motor/movement, and mental abilities.

WHAT IS EXPECTED IF I TAKE PART IN THIS STUDY?

- Attend an in-person screening session, review consent form; with a member of our research team.

- Meet with study nurse to have baseline blood drawn for study medication and safety labs.
- Meet with study physician for physical and psychological evaluation.
- If you are eligible, you will be invited to participate in the three test sessions.
- We will schedule the three test sessions separated by at least 72 hours. If you cannot keep an appointment, please call our research team as soon as can to reschedule.

- On the test days, your methadone or buprenorphine morning dose will be temporarily held,and administered after the study assessments. If you receive methadone/buprenorphine from a non-VA opioid treatment program, study staff will work with your clinicians, to make sure that you are able to bring your medication to be given in the study session.
- The 2 hours before coming to the test session you can drink your usual amount of coffee.
- We ask that you do not eat on the morning of the test session. At the end of the test session, you will be given both a light, low-calorie, low-fat snack and a beverage that do not contain caffeine.
- You will not be able to smoke while you are in the test room. You may not use illicit drugs, alcohol, or pain killers.
- A pregnancy test will be given before each test session, if you think you're pregnant tell staff as soon as possible.
- We may perform repeated urine drug screenings and breathalyzers.
- Take the study drug as directed; each day you will be assigned a dose of CBD that is a little higher (400 mg, 800 mg, 1200 mg). The medication will be given in a liquid form, by mouth.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Do not drive to and from the study sessions. You must confirm transportation prior to each test session. You will be provide with compensation to cover transportation home.
- Following each study session, research staff will contact you by phone on the same day, to inquire about any side effects of the study medication.
- Please do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from extra blood drawing, or from potential drug interactions, among other potential overlaps between studies.
- Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.
- A physician will verify your medication list for any and all potential drug interactions.
- One week after the last study session, you will be contacted by study staff to inquire about your general well-being.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

The risks of participating in the study include the side effects of CBD, blood collection, and loss of your confidential information. Details of these risks are described below.

Effects of CBD: Epidiolex is an form of CBD that is used to treat childhood seizures. The effects of CBD are different than those of THC, the main ingredient of marijuana. Unlike THC, CBD does not cause a feeling of "high". The effects of CBD may include lower anxiety, as well as lower blood pressure.

The most common side effects of CBD are: sleepiness, low appetite, loose stools, liver damage, weakness, skin rash, and difficulty sleeping. The CBD liquid we give also contains sesame oil. You cannot participate in this study if you are allergic to sesame seed or its products. You cannot participate in the study if you are taking marijuana products, which may contain either THC or CBD.

How your body handles marijuana products *taken by mouth* differs from *smoked* marijuana. While the effects of smoked marijuana usually start immediately, CBD's effects are delayed by 30-120 minutes when it's taken by mouth. Further, the effects marijuana products are more prolonged when they are taken by mouth. The effects of CBD are expected to reach their peak after 90 minutes after administration, and go away within approximately 6-8 hours.

Although CBD has been FDA-approved for children with epilepsy, it has not been studied among people with opioid use disorder and chronic pain who are receiving methadone or buprenorphine.
This is the first study to administer CBD in combination with methadone or buprenorphine, and will help determine the dose of CBD that is safe to administer with opioids in larger studies.

We are taking a number of precautions to reduce the chance of you having an unpleasant response. These precautions include:

- A research nurse will be present throughout the study to check for any changes in your physical or mental state. The research psychiatrist will be present if there are any serious changes in your physical or mental state. The research nurse will also offer support and discuss the progress of the test day, in case the study drug causes confusion.
- We will ask you to remain in the testing area for several hours after the effects of study medications are expected to wear off.
- We will review the test day with you to deal with your feelings and reactions to each test.
- You must have a ride home, or we will arrange transportation by taxi.

- A psychiatrist will be available all day and all night if unexpected, unpleasant effects emerge.

- If you have any side effects that do not go away by the end of the testing, we will stop testing and work with you until these effects have subsided.
- Hospitalization may or may not be necessary until your condition has stabilize to the point that study doctor feels it is safe for you to be discharged.
- The status of your liver will be checked during the study, since CBD and opioids are processed by the liver.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience an unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care. You may not participate in this study if you are pregnant.

- (1) Temporarily Holding the Morning Dose of Methadone or Buprenorphine

  On the test days, the methadone or buprenorphine will be temporarily held, and given later in the morning. Given that methadone and buprenorphine stay in your body for long periods of time (days), we do not expect you to experience opioid withdrawal. If participants experience psychological discomfort from temporarily withholding their medication, they may choose to voluntarily stop their participation.

- (2) Questionnaires

  Some people may become uncomfortable with being asked questions about their drug use or medical history. If, for any reason, you wish not to answer specific questions, or you wish to terminate the session, you will be able to do so.

- (3) Photographs, audiotaping, or videotaping

  There will be no photographs, audio tapes, or video tapes made of you as part of this study

- (4) Inclusion of Women of Childbearing Potential

- (5) Blood drawing

Over the course of the study, you will have about 175 ml (3/4 of a cup) of blood drawn. There will be blood draws in this study, one at screening and three blood draws in each lab session. The blood drawing may cause some pain, bruising or, rarely, infection.

- (6) IV line placement.

Also, we will establish an intravenous cannula on one of your arms to draw blood during the test sessions, which carries additional risk of infection.

The safe use of CBD in pregnant women and nursing mothers has not been established. Consequently, there may be unknown risks to you – or to your embryo or fetus, or if you are nursing – if you are pregnant, or may become pregnant during the study. Women of who can have children and are sexually active enrolling in this study must (i) have been acceptable birth control for the past three months, (ii) must have a negative pregnancy test before each test session, and (iii) must agree to continue to use a birth control measure for the duration of the study. Acceptable birth control for women includes oral birth control pills, birth control injections, birth control implants under the skin, intrauterine devices (IUD), or surgical birth control methods. If, while participating in the study, you suspect you have become pregnant, please contact the study physician immediately.

Women are considered to be able to have children unless they have been sterilized by surgery (for example, ligation or the tubes, or removal of the uterus) or if they had no menstrual period for more than 6 months. Nursing mothers may not participate in this study.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

There are no direct/personal benefits to you from your taking part in this research study. However, the information we get from this study might help others with your condition.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Participation in research may involve a loss of privacy. Your research records will be kept as confidential as possible. A code number will identify your research records. The code number will not be based on any information that could be used to identify you – for example, social security number, initials, birth date, etc. Computer records related to you or your family members, information that could be used to identify you individually will be stored only on a separate protected VA server.

All research information will be secured in locked files. Your identity will not be revealed in any reports or publications resulting from this study. Only authorized persons will have access to the information gathered in this study. Authorized persons may include regulatory agencies such as the Food and Drug Administration, (FDA), the Government Accountability Office (GAO), or the Office for Human Research Protection (OHRP), Office of Research Oversight (ORO), National Institute of Health (NIH), as well as members of the Research Administrative staff of VA Connecticut. The Department of Veterans Affairs (VA) requires some information to be recorded in the VA electronic medical record for all veteran and non-veteran research subjects. The data collected as part of this study may be made available to the VA, FDA, and NIH. A medical record will be created, if you do not already have one. Notes from your visits, procedures, and laboratory tests will be included in this record.

Identifiers can be removed from private information or blood/urine samples that are collected. After that removal, the information obtained by blood/urine samples will be used in the analysis of this study.

We are in the process of obtaining a Certificate of Confidentiality from the Federal Government. This helps protect your privacy by allowing us to refuse to release your name or other information outside of the research study, even by a court order. The Certificate of Confidentiality will not be used to prevent disclosures to local authorities of child abuse or neglect, or harm to self or others. The Certificate does not prevent you or a member of your family from releasing data about yourself or your involvement in this study.

The VA requires some information to be recorded in the VA electronic medical record for veteran and non-veteran research subjects. Therefore, if you participate in this study, a medical record will be created if you do not already have one. Notes from your visits, procedures, and laboratory tests will be included in this record. In addition to the research team, and the VA staff who provide clinical services, other researchers may be granted approval to access this information in the future.

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 at any time.

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. This is not a treatment study, so no it does not include any treatments. If you usually have co-payments for VA care and medications, you will still have these co-payments for VA care and medications that are not part of this study.

Storage and Future Use of Data: Your information or blood/urine sample collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

IS THERE PAYMENT TO ME IF I TAKE PART IN THIS STUDY?

- Either you will be compensated in cash for participating in this study or a check will be processed for your compensation. The compensation will be processed at the end of each test visit.
- Compensation will be $50.00 for screening plus $200 for each of the three test sessions, and $20 dollars for travel to each test sessionif you come to the session on time and take your study medication. The total compensation for the screening session and the three test sessions is $710.
- If you refer people you know who might be interested in the study to the research clinic, you will receive additional $20 for each referred person who is enrolled in the study (e.g., if they meet the study eligibility criteria).

- If you withdraw from the study or terminated from the study, you will only be compensated for the visits you participated in prior to withdrawing.
- You will not be compensated if you do not refrain from alcohol or drugs. The VA preferred payment will be made through an electronic funds transfer (EFT) system. You will be asked to provide your banking information by completing a special payment form. If your banking information changes while you are still participating in the study, you will need to fill out the form again. It is your responsibility to notify us if your banking information changes. Alternatively, if you do not have a bank account or do not wish to provide us with your banking information, a check will be mailed to you instead. This check (s) will be mailed to the address you provide. The process of checks can take a minimum of 1-3 weeks.

- Please, note study payments maybe subject to withholding for outstanding federal debts (i.e. defaulted student loans, interstate child support, back taxes etc.) without notification.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

If you are injured as a direct result of your participation in this research study, VA will provide treatment for research related injury in accordance with applicable federal regulations (38 CFR 17.85). Except in limited circumstances, this medical treatment will be provided in a VA Medical facility. There are no plans to provide compensation for disability or other losses over the long term, or if an injury becomes apparent after your participation in the study has ended. However, by agreeing to participate in this research study, you are not waiving or giving up any legal rights to seek compensation.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY: Dr. Joao P. De Aquino, M.D. 203-932-5711 ext. 2916.

AFTER HOURS: Psychiatric Emergency Room at the VA Connecticut Healthcare System and ask for the Substance Abuse Research Psychiatrist at (203) 932-5711, extension 4472 after hours.

Emergency and ongoing medical treatment will be provided as needed.

DO I HAVE TO TAKE PART IN THE STUDY?

Participation in this study is voluntary.

Refusal to take part in the study will involve no penalty or loss of benefits or rights to which you are otherwise entitled.

You may withdraw from the study at any time without any penalty or loss of benefits.

If you choose to withdraw from the study, no additional follow-up visits will be requested.

If you withdraw from the study, the study cannot collect further information from you, but the data already collected prior to your withdrawal will still be retained and used for research study purposes.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

Your participation in this study may be stopped any time during the study without your consent if: 1) the study physician/medical monitor decides that continued study participation may cause physical or psychological harm to you; or 2) you become unable or unwilling to fulfill the scheduled visits and procedures.

If your participation is terminated, you will still be compensated for the visits you already participated in. We do not expect withdrawal from the study to have any undesired effects on your health or welfare, since this is not a treatment study. If you are withdrawn from the study, no additional follow-up visits will be requested.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

- If you have questions about your rights as a study subject, or you want to make sure this is a valid VA study, you may contact the Chairman of the Human Studies Subcommittee at 203-932-5711 x3350.
- If you have questions about the research and use of private information or biospecimens you may call the Principal Investigator, Dr. Joao P. De Aquino, at 203-932-5711 ext. 2916.
- In the event of a research-related injury to yourself, you may call the Human Studies Subcommittee Coordinator at 1-203-937-3830.

If you have questions about your rights as a study subject, or you want to make sure this is a valid VA study, you may contact the Chairman of the Human Studies Subcommittee at 203-932-5711 x3350.

If you have questions, complaints or concerns about the study or if you would like to obtain information or offer input you may call the Principal Investigator, Dr. Joao P. De Aquino, at 203-932-5711 ext. 2916.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

You will be informed of any new findings developed during the course of the research that may affect your willingness to continue participation.

You will be informed of results of clinical relevance or concern (e.g., positive pregnancy test, high blood pressure) are found during your screening session or study participation.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

A member of the research team has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study You also confirm that you have read this consent document, or it has been read to you. You will receive a copy of this consent document after you sign it.

I agree to participate in this research study as has been explained in this document.		
_____ Subject's Name	_____ Subject's Signature	_____ Date

_____ PI or Person Obtaining Consent	_____ PI or Person Obtaining: Signature	_____ Date