Study Title: Clinical Study to Evaluate Cannabidiol Liver Enzyme Elevations and Drug Interactions

Document Title: Informed Consent Form – Study No. SCR-016

Document Date: 10 May 2024

NCT Number: NCT06192589

CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Sponsor/Study Title:	**U.S. Food and Drug Administration, Clinical Study to Evaluate Cannabidiol Liver Enzyme Elevations and Drug Interactions**
Protocol Number:	**SCR-016**
Principal Investigator: (Study Doctor)	**Melanie Fein, M.D.**
Telephone:	**800.597.4507 (Recruitment Department)** **855.622.8100 (24-hour urgent question/care)**
Additional Contact(s):	**Trupti I., Project Manager** **Karrielynn G., Study Manager** **Samuel B., Associate Study Manager**
Address:	**Spaulding Clinical Research, LLC** **525 S Silverbrook Dr.** **West Bend, WI 53095**

SUBJECT SCREENING #_____

Please read this form carefully. Take time to ask the study doctor or study staff as many questions about the study as you would like. The study doctor or study staff can explain words or information that you do not understand. Reading this form and talking to the study doctor or study staff may help you decide whether to take part or not. If you decide to take part in this study, you must sign your name at the end of this form. You cannot take part in this research study until you sign and date this form.

WHAT IS A VOLUNTEER INFORMED CONSENT?

You are being asked to take part in a research study which will look to characterize the effects of daily cannabidiol (CBD) for 4 weeks at a dose within the range of what consumers are taking with unapproved CBD on liver enzyme elevations, drug interactions, and endocrine hormones.

For the drug-drug interaction (DDI) studies, approved Food and Drug Administration (FDA) drugs will be used. These drugs are morphine and citalopram. However, the use of these drugs in this study in combination with CBD is investigational.

Before you decide to take part, you should understand the possible benefits and risks associated with this study. This process is known as informed consent and means that you will:

- Receive detailed information about this research study.
- Have a chance to ask and receive answers to any questions you may have.
- Be asked to read and sign this informed consent once you understand the study and wish to take part.

- Be given a signed and dated copy of this informed consent to keep.

Taking part in this study is entirely voluntary.

WHY ARE THESE DRUGS BEING STUDIED?

The cannabis plant contains bioactive compounds known as cannabinoids; delta-9 tetrahydrocannabidiol (THC) and cannabidiol (CBD) are the most prevalent cannabinoids in most varieties of cannabis. CBD is available as a prescription drug product for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex (Epidiolex is the name of the CBD product and is approved by the FDA for certain seizure disorders. At labeled doses up to 25 mg/kg/day, an increased risk of liver enzyme elevation has been observed. However, only limited evaluations of the risk of liver enzyme elevation of daily, lower dose CBD use are available. The potential for liver enzyme elevations with CBD doses in unapproved consumer products highlights a need for further research to quantify risks at these doses. In addition, CBD has the capacity to inhibit cytochrome P450 enzymes and uridine 5'-diphospho-glucuronosyltransferases, leading to potential drug-drug interactions with multiple common medications. The clinical significance of many of these interactions is also unclear. Furthermore, nonclinical studies have suggested the potential for CBD to cause reproductive and endocrine effects. As such, additional high-quality clinical pharmacology studies are needed to further characterize CBD's safety profile.

Citalopram (Celexa) is a selective serotonin reuptake inhibitor (SSRI) indicated for treatment of major depressive disorder. Citalopram (Celexa) is orally administrated and available as 10 mg, 20 mg, and 40 mg strength tablets. It is a substrate of the metabolizing enzyme CYP2C19 and CYP 3A4 that may be inhibited by CBD.

Morphine sulfate tablet is an opioid agonist indicated for the management of moderate-severe acute and chronic pain. It is available in 15 mg and 30 mg oral tablets. Morphine is primarily metabolized by UDP-glucuronosyltransferase, which may be inhibited by CBD.

WHO IS BEING ASKED TO TAKE PART IN THIS STUDY?

Approximately 240 healthy male and female adult subjects, who meet the requirements following a screening visit, will be enrolled in the study. This study will be divided into 2 parts. The first part, in which only CBD is administered will consist of 200 total subjects. Part 2, in which drug interactions will be studied with citalopram and morphine, will include 40 subjects.

You have been asked to take part in this study because you are in general good health, are 18-55 (inclusive) years of age, have no history of heart or liver disease or other significant medical conditions, no history of allergies, and have not participated in another research study for an experimental drug (or a medical device) within 30 days of the first dose of study drug.

HOW MUCH TIME IS REQUIRED TO TAKE PART IN THE STUDY?

If you decide to take part in the study, you will be asked to attend a screening visit. If you pass the screening visit, you will return to the clinic for 2 inpatient stay periods. If selected to participate in Part 1 of the study, each in-house period will last for 2 days and one night. Clinic visits will occur weekly for the three weeks between these inpatient visits. There will be a final clinic visit 6 days after the final inpatient stay. For Part 2 (the drug-drug interaction study), subjects will be assigned to a citalopram cohort (cohort also known as group) or a morphine cohort. For the citalopram cohort, the two inpatient

stays will be 7 days and 6 nights. The second inpatient stay will begin 6 days after the check-out from the first inpatient stay. For the morphine cohort, the first inpatient stay will be 7 days and 6 nights, while the second inpatient stay will be 4 days and 3 nights. The second inpatient stay will begin 4 days after the check-out of the first inpatient stay. The final clinic visit will be on Day 24 for the citalopram group and Day 19 for the morphine group.

The duration of your participation in the study from check-in to final follow-up will be up to 36 days if placed into Part 1 and up to 25 days if placed into Part 2.

You may be asked to return to the clinic for follow up visits in 24-48 hours for additional liver function monitoring if liver function tests are elevated based on study doctor's recommendations. These visits may continue every 24-48 hours or change to twice weekly or weekly depending on the values of the tests and/or if the values are worsening or improving. If your liver function values do increase additional testing may be required for other possible causes such as Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, and Hepatitis E and a number of other viruses. Hepatitis test results will be reported to the health authorities as required by state law.

INFORMATION FOR FEMALE SUBJECTS

You should not screen for this study if:

There is any possibility that you may become, or are pregnant,

- You have given birth in the last 3 months, or
- You are breast feeding.

You may screen for this study if you meet one of the following criteria:

- You are of non-childbearing potential (non-childbearing potential includes post-menopausal females and females who have undergone a hysterectomy)
- You have been strictly abstinent for 1 month before check-in (Day -1) and agree to remain strictly abstinent for the duration of the study and for at least 1 month after the last administration of study drug.
- You are using two adequate methods of contraception (birth control) to avoid pregnancy throughout the study and for at least 3 months after last study drug administration.

Adequate methods of contraception include use of two of the following categories of which one (1) must be a barrier method from Screening until at least 1 month after the end of the study.

- Hormonal implants/patch,
- Oral hormonal contraceptives,
- Injectable hormones,
- Intra-uterine device (IUD),
- Approved cervical ring,
- Diaphragm with spermicide or condom (female or male) with spermicide

The use of spermicide alone and condom alone are not acceptable methods of contraception.

Except for continuous abstinence (no sexual intercourse with a male partner), no method of birth control can be considered 100% reliable in preventing pregnancy. Although the risk of becoming pregnant is low with many methods, unplanned pregnancies may occur with all birth control methods. Most occur because of improper or irregular use of the birth control method. If you are usually not sexually active but become sexually active, you must follow the advice documented above regarding contraceptive methods.

All females enrolled in this study will have a pregnancy test performed at screening, before admission on Day -1 and the follow-up clinic visit on Day 35 (Part 1), Day 24 (Part 2- Citalopram cohort) or Day 19 (Part 2- Morphine cohort) and/or early exit visits.

Please be aware that a pregnancy test may not be positive until 12 days after conception (fertilization of the egg by sperm). Therefore, if you do not follow the study birth control requirements and/or your birth control method has failed, you will not be able to count on a negative test to confirm that you are not pregnant.

If you know that you have not followed the study birth control requirements outlined above, then you must immediately inform us. You must not take any dose of the study drug if you have not followed these requirements.

INFORMATION FOR MALE SUBJECTS

You must agree to practice 2 highly effective methods of birth control (condom with spermicide) from check-in (Day -1) until at least 3 months after the last dose of study drug. The effect of the study drug on male sperm is unknown. In rare cases, drugs may damage sperm in ways that affect a child that is fathered. Male subjects may not donate sperm for 90 days after the end of the study.

Periodic abstinence and withdrawal are not acceptable methods of contraception.

HOW WILL YOU KNOW IF YOU ARE ELIGIBLE TO TAKE PART?

You will need to fast for at least 8 hours prior to your arrival at Spaulding Clinical Research, LLC. for your screening visit, meaning you should not eat any food and should only have water to drink.

At the beginning of the Screening visit, Informed Consent will be obtained.

Before starting the study, the following screening procedures will be performed:

- A complete medical history and physical examination (including height and weight measurements for Body Mass Index [BMI, a way to tell if your weight is proportional to your height]).
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- A complete history of relevant allergies or drug sensitivities.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- You will be asked if you have taken any medication recently.
- You will be asked if you have been feeling ill recently.
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, cotinine test and pregnancy tests (all female subjects), and testing for HIV, hepatitis B and C. Positive results of HIV or any hepatitis tests will be reported to local health authorities as required by state law.

If you meet the "entry criteria" of the study, according to the study doctor, you will be tested again when you are admitted to Spaulding Clinical Research, LLC. You will have the entry criteria reviewed again to ensure that you still are eligible for the study.

In addition, prior to admission you will have a diagnostic test performed to detect severe acute respiratory syndrome coronavirus 2 (called "coronavirus" from now on), which is the virus that causes COVID-19. Depending on the time required to return results, this may be performed ~2 days before check-in or may be performed on the check-in day. You will only be allowed to be admitted if your

coronavirus test is negative. A positive result may be reported to local health authorities as required by state law. In addition, when entering the building for screening and check-in, triage for COVID-19 will take place. The exact details of what will occur at triage may change as additional information or testing is available, however as of now it is planned to include asking about any potential contacts with COVID- 19, signs and symptoms associated with COVID-19, temperature monitoring and antigen screening for coronavirus. You may need to be tested for COVID 19 several times during the study, upon admission, prior to discharge or if you develop symptoms during the study.

HOW WILL THE STUDY BE DONE?

Approximately 240 healthy adult subjects, both male and female will be enrolled in this study. The study will consist of two parts. Part 1 of the study includes 200 subjects evaluating liver tests, and reproductive and thyroid hormones. Part 2 will study 40 subjects for CBD drug-drug interactions.

Part 1

Day -1	CBD Dosing Days 1-28 (5mg/kg/day)					Day 29	Day 35
	Day 1	Day 7	Day 14	Day 21	Day 28		
Check-in	Check-out	Clinic visit 1	Clinic visit 2	Clinic visit 3	Check-in	Check-out	Follow-up visit (Clinic visit 4)

Part 2

Citalopram DDI cohort

Day -1	Day 1	CBD Dosing Days 6-17 (5 mg/kg/day)			Day 18	Day 24
		Day 6	Day 12	Day 13		
Check-in	DDI drug Dosing (baseline)	Check-out	Check-in	DDI drug Dosing (w/ CBD)	Check-out	Follow-up visit

Morphine DDI cohort

Day -1	Day 1	CBD Dosing Days 4-12 (5 mg/kg/day)				Day 13	Day 19
		Day 4	Day 6	Day 10	Day 11		
Check-in	DDI drug Dosing (baseline)	DDI drug Dosing (w/ CBD)	Check-out	Check-in	DDI drug Dosing (w/ CBD)	Check-out	Follow-up visit

Once the study doctor determines that you are eligible to participate, you will be enrolled into Part 1 or 2. You will not be allowed to choose your part in which you receive the study treatments. Part 1 will be a double blinded study, neither you nor the study doctor or study staff will know which study treatment you are receiving—study drug or placebo. A placebo is a medically inactive substance which looks like the study drug.

You will go through the same tests and procedures described below for any of the study treatments you receive.

WHAT TESTS AND PROCEDURES WILL BE USED IN THE STUDY?

Check-in (Part 1: Days -1 and 28, Part 2 (Citalopram): Days -1 and 12, Part 2 (Morphine): Days -1 and 10)

Upon admission to Spaulding Clinical Research, LLC., you will be given an identity band to wear throughout your entire stay in the unit.

You will need to fast for at least 8 hours prior to your arrival at Spaulding Clinical Research, LLC. for your check-in, meaning you should not eat any food and should only have water to drink.

The following admission procedures will be performed:

- Perform/review results from coronavirus test.
- Medical history updates.
- Physical examination.
- Clinical laboratory tests (urine and blood samples), including screening for drugs, alcohol, cotinine test and pregnancy tests (all female subjects).
- Assessment of blood pressure, respiratory rate, heart rate, and oral temperature.
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart).
- You will be asked for details of any medication taken since the screening or previous visit.
- You will be asked if you have been ill since the screening or previous visit.
- You will be asked if you complied with study restrictions.
- You will be provided meals (lunch, dinner, and a snack).
- Inclusion/Exclusion assessment and preparation for randomization (Part 1). Randomization means that you will be assigned by chance, like the flip of a coin, to either study group.

The results from these tests will help the study staff determine whether you are still eligible to enter the study.

In-house Study Treatment Period (Part 2 (citalopram): Days 1-5 and Days 13-17, Part 2 (morphine): Days 1-5 and Days 11-12)

- Adverse event (side effect) assessment and changes in concomitant medications
- Study drug administration
- Assessment of blood pressure, heart rate, respiratory rate, and oral temperature
- Physical examination
- Pharmacokinetic (PK) blood sampling
- Clinical laboratory tests (blood sampling)
- Meals

Check Out (Part 1: Days 1 and 29, Part 2 (citalopram): Days 6 and 18, Part 2 (morphine): Days 6 and 13)

- Adverse event assessment and changes in concomitant medications
- Physical examination
- Pharmacokinetic (PK) blood sampling
- Clinical laboratory tests (blood sampling)
- Assessment of blood pressure, heart rate, respiratory rate, and oral temperature
- After first checkout study medication will be provided for the time to the next clinic visit

At-home Study Treatment Period (Part 1: Days 2-6, 8-13, 15-20, and Days 22-27, Part 2 (citalopram): Days 7-11, Part 2 (morphine): Days 7-9)

- Twice-daily at-home study product dosing (taken with meals)

Daily reminder texts will be sent to remind you to report any adverse events, changes in concomitant medications, and/or dosing concerns. You should not reply to the text message with any updates, but instead please call to report any adverse events, changes in concomitant medications and/or dosing concerns.

Clinic Visits (Part 1: Days 7, 14, and 21)

- Adverse event assessment and changes in concomitant medications
- Pharmacokinetic (PK) blood sampling
- Meal
- Clinical laboratory tests (blood sampling)
- Assessment of blood pressure, heart rate, respiratory rate and oral temperature
- Administration of study product
- Study drug dosing and study drug until next visit

Follow-up (Part 1: Day 35, Part 2 (Citalopram): Day 24, Part 2 (Morphine): Day 19)

- Adverse event assessment and changes in concomitant medications
- Clinical laboratory tests (urine and blood samples) including pregnancy testing for all female subjects
- Physical examination
- Pharmacokinetic (PK) blood sampling
- Assessment of blood pressure, heart rate, respiratory rate and oral temperature
- An electrocardiogram (ECG), (a painless recording of the electrical activity of your heart)
- Discharge from Spaulding Clinical after all events are completed

At-home study treatment requirements and restrictions

- Dose diary completion (completed after each at-home dose has been administered)
- Dose is required to be stored in an area children can't access, the dose will not be in child safety packaging
- Dose should be taken after eating breakfast and dinner at consistent times
- Do not drive or operate heavy machinery until you know how the cannabidiol affects you

End of Study/Follow Up Procedures

- If you leave the study early, you will be asked to have all end of study procedures completed and required follow up procedures based on study doctor's recommendations.

WHAT TESTS AND PROCEDURES WILL BE USED IN THE STUDY?

Blood Sampling

Pharmacokinetic (PK) blood samples will be collected for the measurement of levels of epidiolex, citalopram, morphine, and respective metabolites.

If assigned to Part 1, approximately 6 PK blood samples will be taken on the following days:

- Check-out Day 1, Clinic visit Day 7, clinic visit Day 14, clinic visit Day 21, check-out Day 29, and at follow-up on Day 35

If you are assigned to Part 2 (citalopram cohort) approximately 26 PK samples will be collected as follows:

- 13 PK samples over 120 hours will be obtained during each in-house stay
    - Days 1 and 13: 8 PK samples
        - 0, 1, 2, 3, 4, 6, 8, 12 hours
    - Days 2 and 14: 1
        - 24 hours
    - Days 3 and 15: 1
        - 48 hours
    - Days 4 and 16: 1
        - 72 hours
    - Days 5 and 17: 1
        - 96 hours
    - Days 6 and 18: 1
        - 120 hours

If you are assigned to Part 2 (morphine cohort), approximately 39 PK samples will be collected as follows:

- 13 PK samples over 48 hours will be obtained for each morphine drug interaction assessment
    - Days 1, 4 and 11: 11 PK samples
        - 0, 15, 30, 45, 60, 90 minutes
        - 2, 3, 4, 6, 12 hours
    - Days 2, 5 and 12: 1
        - 24 hours
    - Days 3, 6 and 13: 1
        - 48 hours

Each blood sample will be labeled with subject number, study number, study day, time point, event, and a barcode that matches that belonging to the subject.

- For Part 1, separate blood samples will be collected for measurement of hormones, proteins, and lipids (e.g., cholesterol) in your blood prior to dosing on Day 1 and at check-out on Day 29. An additional blood sample on study days 1, 14, and 28 will also be collected to provide serum samples for cytokine and antibody testing. These blood samples will be processed to be used in cytokine (a type of protein that is made by certain immune and non-immune cells and has an effect on the immune system) and antibody (proteins that protect you when an unwanted substance enters your body) level testing.

- For Part 2, an additional blood sample will be collected on the following days to provide serum samples for cytokine and antibody testing:
    - Morphine cohort: pre-dose, Day 4, Day 10, and Day 13
    - Citalopram cohort: pre-dose, Day 6, Day 12, and Day 18

These blood samples will be processed to be used in cytokine (a type of protein that is made by certain immune and non-immune cells and has an effect on the immune system) and antibody (proteins that protect you when an unwanted substance enters your body) level testing.

You will have numerous blood samples drawn during the entire study for study drug levels as shown

above, and 8 (Part 1) or 3 (Part 2) safety laboratory draws throughout the study. The blood samples may be taken by individual needle sticks into one of your arm veins, or, if necessary, by an indwelling catheter (a thin plastic tube placed in a vein in your arm). Additional blood samples may be obtained for safety reasons throughout the study based on the study doctor's recommendations. Two tubes of blood will be drawn to store for the duration of the study and in the event, you test positive for an infection during the study we may test the tube of blood to compare the results to assess if you already had an existing condition. At the conclusion of the study, if not used, these tubes will be destroyed.

Total number of blood samples for Part 1 will be approximately 19, for Part 2 citalopram cohort 33, and for Part 2 morphine cohort 46.

If your liver function tests are elevated the study doctor or designee may recommend return visits that will include additional safety labs. The total blood volume for the safety labs associated with each visit will be approximately 21 mL or about 4 teaspoons/

The total amount of blood taken for the entire study will be approximately 156 mL or a little more than 0.5 cup for Part 1, 258 mL or about 1 cup for the citalopram cohort of Part 2, and 333 mL or about 1.5 cups for the morphine cohort of Part 2.

GENETIC TESTS

A blood sample will be collected in both Parts for genetic testing.

Participating in the study is optional but in order to be included in the study you must agree to the genetic testing. If you do not agree to the genetic testing please do not sign the consent form as you will not be able to participate in the study.

This genetic test will be exploratory by nature and the results may or may not be reported in the study documentation. Genetic testing is done to study differences in how our bodies respond to or handle drugs. This research will look at genetic differences to better understand why people react or respond differently when they get the same drug. Any personal health information about you, including any genetic information, will be kept confidential. Your personal information will not be attached to the sample.

Privacy Risks

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

• Health insurance companies and group health plans may not request your genetic information that the sponsor will get from this research.
• Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
• Employers with 15 or more employees may not use your genetic information that the sponsor will get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans and all employers with 15 or more people must follow this law.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance or long-term care insurance.

POSSIBLE BENEFITS

There is no direct benefit to you from participating in the genetic test. Your participation in the genetic test may help find better ways to treat diseases in the future. This may also help doctors and scientists understand why people react to drugs differently. This research may help identify who is more likely to respond to different drugs and who may experience side effects.

Please ask the study staff to explain any words or information about the genetic testing you do not understand.

WITHDRAWAL FROM STUDY AND REFUSAL TO PARTICIPATE

If you consent to the genetic test and decide at a later date that you would like to withdraw your consent, you will need to do so by contacting your study doctor at the address listed on the first page of this consent form.

Withdrawing consent will result in destruction of your genetic sample(s). However, if you withdraw your consent after the sample has been tested, the test results and research study/sample-related information must remain in any database(s) that were created for the research study. The reason for this is to comply with regulations that require us to make data available for review by the United States Food and Drug Administration (FDA) or other appropriate regulatory authorities, or if this research is used to support an application for FDA approval to market the study drug.

If you withdraw consent for participation in the study or are discontinued (withdrawn) from the study, the sample you provided for genetic testing will continue to be available for testing unless you also withdraw your consent for the genetic test as stated above.

Urine Sampling

You will have urine samples collected at screening, first check-in day (Day – 1), each subsequent check-in for overnight stays (Part 1: Day 28 and Part 2: Day 12 or Day 10) and on the final follow-up visit (Part 1: Day 35 and Part 2: Day 24 or Day 19). These will be used to screen for either alcohol or drugs, and for routine safety analysis. Additional urine samples, which may include urine drug screens, may be obtained for safety reasons throughout the study based on the study doctor's recommendations.

ECG Measurements

Safety ECG measurements will occur at screening, check-in day (Day -1) and on the follow-up visit (Part 1: Day 35 and Part 2: Day 24 or Day 19). Additional ECG measurements may be obtained for safety reasons throughout the study based on the study doctor's recommendations.

Some individuals may develop redness, irritation, skin breakdown or discoloration of the skin at the site of ECG electrodes placed on the chest/body. This may develop due to sensitivity to the electrodes or to our skin preparation procedure. In order to get the quality results we need, it is necessary for us to lightly scrub the skin with an abrasive pad to remove any skin impedance such as oil, dead skin cells and lotions.

WHAT ARE YOUR RESTRICTIONS DURING THE STUDY?

You will need to avoid the following while taking part in this study, and most importantly from the time of your screening visit until you check in: In the event you are prescribed any medication by a treating provider or facility, it is important that you notify that provider that you are taking Epidiolex. Do not continue taking the Epidiolex without speaking with the study doctor.

Restricted Item:	**Duration:**
Alcohol, Marijuana or marijuana-derived products, hemp or hemp-derived products, including CBD (except for provided study drug), and illicit drugs of any kind.	Refrain from using any for the duration of the study.
Caffeine or other xanthine containing products (for example, coffee, tea, cola or chocolate)	24 hours prior to check-in until final check out.
Grapefruit/grapefruit juice/grapefruit hybrids, pomelos, cranberries, pomegranates, star fruit, Seville oranges, apples, vegetables from the mustard green family (for example, kale, broccoli, watercress, collard greens, brussels sprouts, mustard) and charbroiled meats	24 hours prior to check-in until final check out.
Prescription medication	14 days prior to dose until final check out.
Aspirin or NSAIDs (example Ibuprofen, Naproxen)	14 days prior to dose until final check out unless approved by the study doctor
Complementary and alternative medicines	28 days prior to first dose of study drug until final check out.
Nicotine containing products: e.g., cigarettes, cigars, chewing tobacco, snuff, electronic cigarettes	6 weeks prior to screening until final check out.
Participation in another clinical study of an investigational drug or treatment with an investigational drug.	30 days prior to screening until final check out.
Acetaminophen	Refrain from using for the duration of the study unless approved by the study doctor.
St Johns wart or Kava melatonin	Refrain from using for the duration of the study.

You will receive a diet that does not contain any alcohol or caffeine. You may be required to eat each meal that is served to you and eat at a reasonable pace (within 25 minutes).

A fasting period of 8 hours will be required prior to lipid profile sampling on check-out Days 1 and 29. Additionally, a fasting period of 4 hours will be required before all time points when clinical laboratory samples will be obtained.

You may eat only meals and snacks that are provided to you during the periods of your stay. After checking out of the clinic there are no dietary restrictions aside from what is listed in the table above.

You must be willing to comply with study rules, including the meal schedule (25 minutes to eat), attempting to void at specified times, remaining quiet, awake, undistracted, motionless, and seated during specified times, and avoiding vigorous exercise as directed throughout the duration of the study.

On certain study days you may be required to get up very early (between 4 and 6 am) in order to

complete study events. You may also be required to stay or wake up during the night to ensure study procedures can be completed. This will only be done when absolutely necessary and while it is important that you have sufficient rest during the study sometimes an early start to the day is unavoidable.

Due to current precautions being taken for COVID-19, the following restrictions will be in place:

- Subjects should be encouraged to wear masks except when in a private room without anyone else present or for a limited time for a study procedure (for example, study drug administration) when instructed by study staff.
- Subjects must practice social distancing, which will include having a maximum of 2 subjects per room for overnight stays and access to common areas will be per clinical research site standards. While subjects are in house, meals will be served per clinical research site standards. Subjects will spend most of their time in their rooms except for specified times for walking in the halls (with masks recommended).
- Subjects must practice regular handwashing with soap and water, scrubbing hands for at least 20 seconds or with approved hand sanitizer as supplied by study staff.

If new information becomes available, there could be other precautions that lead to additional restrictions.

ARE THERE RISKS TO YOU IF YOU ARE IN THIS STUDY?

Please be advised that for certain adverse events (AE) we may not administer medications but first try treatments such as heating pack, stretches, or hydration. Our study doctor will be notified if a medication may be needed to treat an AE. Following the study plan guidelines, the study doctor will assess your AE and develop a treatment plan.

A combination of Epidiolex with Morphine or Citalopram may worsen adverse events.

It is dangerous to mix Epidiolex with alcohol or any other drugs, including illicit drugs, certain prescription drugs and over counter drugs such antihistamines that can cause sedation. If you need any treatment by your own doctors or an emergency room advise the medical staff treating you that you are in a research study and the study drug you are taking. <u>You should advise your primary care physicians of your participation in the study**.** If you are prescribed any medication during the study you must notify the study staff prior to taking any additional doses of study drug.</u>

Risks are possible side effects of the study drug, the positive control medicine, and those of taking blood and other medical procedures:

<u>For Cannabidiol (Epidiolex)</u>

- Abdominal effects – liver injury, abdominal pain, nausea, vomiting, diarrhea, and decreased or increased appetite
- Hematologic effects – anemia (Low number of red blood cells that can causes tiredness and shortness of breath)
- Neurological effects – feeling inebriated (drunk), somnolence (sleepiness), insomnia, poor sleep, fatigue (tired), malaise (feeling of uneasiness), depression, suicidal thoughts or behavior, irritable, anger (aggression), asthenia (feeling weak or lacking energy), drooling (increased saliva) or dry mouth, change in sense of taste, muscle spasms, impaired thinking, judgement, motor skills and gait disturbance (difficulty walking)
- Do not drive or operate heavy machinery until you know how the <u>cannabidiol</u> affects you.
- Renal effects – reversible elevation of creatinine (blood test of kidney function)
- Skin effects – rash, redness, itching, and swelling

- General effects – weight loss or gain, fever, infections including pneumonia and urinary tract infections
- Less common side effects include:
    - Lung effects – low oxygen content in blood

For Citalopram

- Abdominal effects – nausea, diarrhea, constipation, and indigestion
- Neurological effects – decreased libido (sexual desire), agitation, headache, dizziness, drowsiness, yawning, suicidal thoughts or behavior, and tremor (shakiness)
- General effects – insomnia, ejaculation disorder, sweating increased, fatigue (feeling tired), somnolence (tiredness), impotence and anorgasmia (difficulty having an orgasm), dry mouth, hair loss, fever, increased sweating
- Less common, but serious adverse events include:
    - Allergic reactions – hypersensitivity reactions, rash, swelling
    - Neurological effects – syncope (fainting), seizures, myoclonus (abnormal muscle movements)
    - Heart/blood vessel effects – QT interval prolongation (abnormal ECG), irregular heartbeat, abnormal blood clotting or bleeding
    - Abdominal effects – increased liver enzymes (possible liver damage)
    - Serotonin syndrome (usually when prescribed with another serotonergic medication which will not be done in this study – leads to fever, sweating, diarrhea and potential complications including seizures and muscle breakdown)

For Morphine sulfate

- Abdominal effects – abdominal pain, nausea, vomiting, diarrhea, constipation, and abnormal liver function tests
- Neurological effects – seizure, headache, insomnia (difficulty sleeping), abnormal dreams (nightmares), asthenia (general weakness), lightheadedness, dizziness, agitation, anxiety, hallucinations, drowsiness (being sleepy), fatigue, tremor (shakiness) or muscle rigidity, amblyopia (double vision), and paresthesia (tingling)
- Skin effects – itching and swelling
- Urogenital effects: decreased libido (sexual desire), abnormal ejaculation, impotence, and urinary retention (difficulty passing urine)
- Less common, but serious adverse events include:
    - Lung effects – respiratory depression/arrest (decreased/stopped breathing)
    - Heart/blood vessel effects – bradycardia (slow heart rate), blood circulatory depression and hypotension (decreased blood pressure), cardiac arrest and/or shock (heart, lung, and circulatory changes that are potentially life threatening)

Problems or side effects that are not now known could also occur. You will be given any new information that may affect your willingness to start or continue in the study. During the study and following the study you may test positive for THC or marijuana, as well as opiates, on a drug screen.

If you have a side effect of the study formulation, such as a skin rash or other visible injury, it might be useful to take a picture of the affected area to send to the sponsor. If the condition is on your face, all reasonable attempts will be made to disguise your facial features and hide your identity. It is possible that your face may be recognizable. By signing this consent, you authorize the study doctor or study staff to take such a picture and provide it to the sponsor.

Suicide is a risk with the use of cannabidiol and citalopram. You must tell your study doctor right away if you have any thoughts about hurting yourself.

If you are having suicidal thoughts or feel in crisis, call the study doctor at the telephone number listed on the first page of this form. You can also call or text the National Suicide & Crisis Lifeline at 9-8-8 or 1-800-273-TALK (8255). The Lifeline numbers are answered 24 hours a day every day of the year by a skilled, trained counselor. You can also present to a healthcare provider, your local emergency room, or call 9-1-1 to be connected to local emergency services.

Additional Risks

As with any drug, it is possible that you could experience an allergic reaction to the study drug used in this study. Symptoms of any allergic reaction can include:

- Rash
- Hives
- Itching
- Difficulty breathing
- Closing of the throat
- Swelling of the lips, tongue or face
- Rarely, death.

If you think you are having a severe allergic reaction, while outside the study center call 9-1-1 and seek medical attention immediately.

It is very important that you tell the study doctor and the study staff about any side effects that you might experience.

You may experience side effects or discomforts that are not listed on this form. Tell your study doctor or study staff immediately if you have any problems. Your safety will be closely monitored during the course of the study.

For Blood Draws

- Fainting
- Redness
- Pain
- Bruising
- Rarely, there may be a small blood clot or infection at the site of the needle puncture

An intravenous catheter (a thin plastic tube placed in a vein in your arm) may be placed at study doctor's discretion to quickly deliver rescue medications in the event of an emergency situation or treatment such as IV fluids are needed.

Intravenous catheter (IV) Risks

- Redness
- Pain
- Infection
- Bruising
- damage to blood vessels
- bleeding from the site of insertion
- swelling in the area
- allergic reaction to the adhesive tape that secures the IV in place
- Rarely, there may be a small blood clots at the site of the needle puncture

In instances where a nurse, a doctor, or a technician, sustains an exposure to your blood, tissue or body fluids by needle stick, cut or splash to mucosa or damaged skin, it may be necessary to test your blood, tissue, or body fluid sample for certain viral infections including Hepatitis B and C and HIV on the sample already available. This is to enable that person to receive appropriate counseling, monitoring and treatment if necessary. In this instance the study doctor or designee will offer you the information relevant to your health and advise you on the next steps. Confidentiality of your data will be respected at all times according to the state law.

For Blood Pressure Monitoring
The blood pressure cuff may also cause discomfort or bruising to the upper arm.

Fasting
Fasting could cause dizziness, headaches, stomach discomfort or fainting

For ECG Monitoring
You will be given a small portable heart monitor to wear. The monitor is connected by wires that are stuck to your chest, using tape or stickers. To attach the monitor wires, a small section of your chest might have to be shaved. You must return the monitor to the study staff. It is possible to be sensitive to the adhesives used on the electrodes that are applied to your chest when having an ECG performed. If this is the case, you could develop a temporary redness, irritation, skin breakdown, or discoloration of the skin where the electrodes were applied.

HIV, Hepatitis B and C, and COVID-19 Testing
The risks of HIV and Hepatitis B and C testing include psychological and social risks. A positive test can lead to restrictions in freedom of travel to some countries and possible prejudices in job employment, insurance eligibility, housing and other forms of discrimination. Positive HIV, Hepatitis B and C, and COVID-19 test results must be reported to health authorities under state law. A positive HIV, Hepatitis B or C and/or COVID-19 result will exclude you from participation in the study.

Reproductive Risks
The effects of the test drug on human pregnancy and the unborn child (fetus) are unknown. Therefore, for females it is very important that you do everything within your power not to become pregnant during this study and for 1 month following last dose. For males it is very important that you do everything within your power not to father a child or donate sperm during this study and for 3 months following the last dose. Please ensure that you follow the study birth control requirements outlined in the sections regarding information for male and female subjects above.

If you become pregnant during the study, you will be withdrawn from the study immediately. Neither Spaulding Clinical Research, LLC. nor the sponsor will be responsible for the cost of any obstetric or related care, or for your child's care. Female subjects are agreeing, by signing and dating this form, that information about your pregnancy and birth of your child may be collected. The information collected will include your health and the health of your unborn child during pregnancy, pregnancy outcome (miscarriage, termination, live birth, etc.), and the health of the baby after it is born (up to 6 weeks after delivery).

Partners of male subjects who become pregnant will be asked to sign a separate consent form to allow collection of the information listed above. Your information will be kept confidential in accordance with state and Health Insurance Portability and Accountability Act (HIPAA) law.

COVID-19 Risks
Despite the extra precautions (for example, COVID-19 triage at screening/check-in, coronavirus testing, mandatory masks for study subjects and study staff, social distancing, extra hand washing) that will be in

place, there is still a risk of developing COVID-19 just as there is when you are not at Spaulding Clinical. Tell your study doctor or study staff about any new symptoms you develop during the study.

The U.S. Centers for Disease Control and Prevention (CDC) currently highlights that people with the following symptoms may have COVID-19:

- Cough
- Shortness of breath or difficulty breathing
- Fever or chills
- Fatigue (feeling tired)
- Muscle or body aches
- Headache
- Sore throat
- New loss of taste or smell
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

It is important to note that COVID-19 can also present with other symptoms and just because you develop any of the above symptoms does not mean that you have COVID-19. Your study doctor will evaluate if your symptoms warrant further isolation from other study subjects/staff, additional coronavirus testing, study termination and/or referral for treatment.

NEW FINDINGS

Your study doctor will tell you of any information learned during the course of the study that might cause you to change your mind about taking part in the study. You may contact the study doctor at any time after your participation ends to find out if any new information about this study has become available.

WHAT IS THE ALTERNATIVE TO BEING IN THE STUDY?

Since this is a study involving healthy subjects, your alternative is not to take part.

WILL YOU BENEFIT FROM TAKING PART IN THE STUDY?

You will not receive direct medical benefit from receiving the study drug. You may benefit by having your medical history recorded, undergoing a physical examination, and having blood and urine tests as they apply to this research project.

Just by taking part in this research study, you may be helping future patients by providing important information about the study drug and by contributing to medical knowledge.

WHO IS PAYING FOR THIS STUDY?

The U.S. Food and Drug Administration is the Sponsor of the study.

The U.S. Food and Drug Administration pays the study doctor to run this study.

The study drug and all tests, procedures, and visits required by the study are provided at no cost to you. The sponsor, the U.S. Food and Drug Administration, pays for them.

Information about this study is confidential. This information belongs to the U.S. Food and Drug Administration. We ask that you keep it private. You can discuss this information in private with your doctor or family to talk about your healthcare or to decide about taking part in this study.

WILL YOU BE PAID FOR BEING IN THIS STUDY?

Compensation for screening is as follows:

- $125.00 if you qualify and take part in a study. $125.00 for your time and inconvenience if you do not qualify for a study.
- If the results of the drug and alcohol tests are positive, or if you attempt to falsify your drug screen you will not receive any compensation.
- If you screen for the study, qualify and are enrolled, your screening payment will be included in your first stipend payment. If you are not accepted into the study your screening payment will be processed and provided within 7 calendar days of study enrollment.

Compensation for this study is as follows:

Part 1

For subjects that complete the entire study (Day -1 to the final follow-up visit), you will receive up to $4800.00. This money covers the costs for time spent at the clinic and is to help cover travel expenses. This payment will be made in 7 separate payments as follows:

- $1200.00 will be paid after all check out procedures have been completed at the end of Day 1 ($600.00/day),
- $360.00 will be paid after all check out procedures have been completed at the end of Day 7,
- $360.00 will be paid after all check out procedures have been completed at the end of Day 14,
- $360.00 will be paid after all check out procedures have been completed at the end of Day 21,
- $1200.00 will be paid after all check out procedures have been completed at the end of Day 29 ($600.00/day),
- $360.00 will be paid after all check out procedures have been completed at the end of Day 35,
- The remaining $960.00 will be paid after the follow up visit, and any additional follow up procedures are completed, and all results are reviewed. Once follow up procedures have been completed and accepted by study doctor your final payment will be processed and provided within 14 calendar days.
    - An additional $200 will be paid for participants who experience elevated liver enzymes and returned for follow-up visits and repeat laboratory assessments as requested by the principal investigator or designee. This will be paid after the final requested follow up visit, all additional follow up procedures are completed, and all results are reviewed. Once follow up procedures have been completed and accepted by study doctor your final payment will be processed and provided within 14 calendar days.

If you withdraw from the study early, you will only be paid for the visits you completed.

Part 2 (Citalopram cohort)

For subjects that complete the entire study (Day -1 to the final follow-up visit), you will receive up to $5875.00. This money covers the costs for time spent at the clinic and is to help cover travel expenses. This payment will be made in 4 separate payments as follows:

- $1763.00 will be paid after all check out procedures have been completed at the end of Day 6 ($252.00/day),
- $1763.00 will be paid after all check out procedures have been completed at the end of Day 18

($252.00/day),
- $1175.00 will be paid after all check out procedures have been completed at the end of Day 24,
- The remaining $1174.00 will be paid after the follow-up visit, and any additional follow-up procedures are completed, and all results are reviewed. Once follow up procedures have been completed and accepted by study doctor your final payment will be processed and provided within 14 calendar days.

If you withdraw from the study early, you will only be paid for the visits you completed.

Part 2 (Morphine cohort)

For subjects that complete the entire study (Day -1 to the final follow-up visit), you will receive up to $4875.00. This money covers the costs for time spent at the clinic and is to help cover travel expenses. This payment will be made in 4 separate payments as follows:
- $1862.00 will be paid after all check out procedures have been completed at the end of Day 6 ($266.00/day),
- $1064.00 will be paid after all check out procedures have been completed at the end of Day 13 ($266.00/day),
- $975.00 will be paid after all check out procedures have been completed at the end of Day 19,
- The remaining $974.00 will be paid after the follow-up visit, and any additional follow-up procedures are completed, and all results are reviewed. Once follow up procedures have been completed and accepted by study doctor your final payment will be processed and provided within 14 calendar days.

If you withdraw from the study early, you will only be paid for the visits you completed.

NOTE: You may be required to return to the clinic for repeat blood test or other assessment (ECG, physical, vital signs) in between periods or after the final check out. This is considered part of the study and no additional compensation is available. Your final payment will not be released until all follow up procedures have been completed and accepted by the study doctor. Once follow up procedures have been completed and accepted by study doctor, your final payment will be processed and provided within 14 calendar days.

NOTE: If you meet eligibility criteria you may be asked to be an alternate subject. Alternate subjects are eligible subjects that are in addition to the number of subjects in the event an enrolled subject drops out before their dose can take place or in the event it is not safe for a subject to move forward with dosing. If you are selected as an alternate subject who has to stay the night in the clinic and you agree to participate as an alternate subject, you may receive up to $250 if you are not needed to dose. If you are selected as an alternate subject and you do not have to stay the night, you may receive up to $150. If you are needed to replace a subject, you will be paid as stated for participating in and completing the study. If you agree to be an alternate subject, you will have all of the predose procedures as the enrolled subjects so that if you are needed, you will be ready to participate. If you are not needed you will be discharged shortly after completion of the dosing round.

No deductions for any state or federal withholding or any other similar taxes will be made and you are solely responsible for reporting such payments on your state and federal income tax returns.

If you need to stay at Spaulding Clinical Research, LLC. For a longer period of time for safety reasons, you will be compensated at a rate proportional to the entire compensation for the study.

If you are dismissed from the study for medical reasons OR if the study is temporarily or permanently halted, your compensation will be proportional to the time you spend in the study.

If you are dismissed from the study because you have not complied with the instructions of the study staff, no compensation is available. Non-compliance includes, but is not limited to, improper conduct, taking alcohol and/or any drugs (including recreational drugs), tampering with the study drug, or consuming any foods/beverages not allowed in the study.

You must follow the inpatient clinic rules of conduct while you are taking part in this study. If you do not follow the rules, a deduction may be taken from your total stipend. You may not be able to take part in future studies at Spaulding Clinical Research. These rules will be reviewed with you at your first inpatient visit.

By signing this consent, you expressly agree that you are an Independent Contractor for Spaulding Clinical Research, LLC. As an Independent Contractor, you will receive a 1099 form from Spaulding Clinical Research, LLC. The 1099 form shall document and report all payments and/or study stipends you received as an Independent Contractor for Spaulding Clinical Research, LLC. In addition, because you are an Independent Contractor and will be receiving payments and/or study stipends, those earnings are subject to wage garnishment. If Spaulding Clinical receives an Earnings Garnishment Notice (or similar) from a State or Federal legal entity, we will adhere to that garnishment.

COMPENSATION FOR INJURY

It is important that you follow carefully all the instructions given by the study doctor and his/her study staff regarding this study.

If you become ill or are physically injured as a result of participation in this study, please contact the study doctor right away at the telephone number listed on page one of this consent form. He/she will treat you or refer you for treatment.

Spaulding Clinical Research, LLC. and/or its affiliated institutions has not set aside funds to provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. You or your insurer will be responsible for the payment of any medical treatments for research related injuries or illness. By signing and dating this consent form, you are not giving up any legal rights. If this research study is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury as you still have the right to seek compensation for injury related to malpractice, negligence, fault, guilt or blame of those involved in the research.

If you are required to stay in the clinic for a longer period for safety reasons, you will be compensated at a rate proportional to the entire compensation for the study. If you become ill or physically injured because of participation in this study, then you will be referred for treatment.

PROTECTING THE PRIVACY OF YOUR HEALTH DATA

Unless required by law, your name will not be disclosed outside the research clinic. Your name will be available only to the following people or agencies: the study doctor and study staff; and authorized representatives of the study doctor; Advarra Institutional Review Board (IRB), health authority inspectors, such as the U.S. Food & Drug Administration and the European Medicines Agency; study monitors and auditors; and authorized Clinical Research Organization representatives. The above-mentioned individuals will use the personal information collected as part of this study, including your medical records (“study information”) to check that the study is conducted correctly and to ensure the accuracy of the study information. These people are all obligated to maintain confidentiality by the

nature of their work or are bound by confidentiality agreements. If required, the study doctor may contact your personal doctor to collect additional medical information and your past medical history.

The study doctor may only share your study information with people whom you have permitted to see it. However, once your study information is shared as authorized, it may no longer be protected by federal law and may be re-disclosed without your permission.

While participating in this study, the study doctor will replace your name with a special code that identifies you. This code, along with your study information, will be used by the U.S. Food and Drug Administration and their representatives, for the study purposes mentioned above and to help establish whether the study drug is safe and effective. Any data and/or biospecimens provided to the U.S. Food and Drug Administration will be coded (stripped of identifiers such as name, address, or account number) and the key allowing the code to be linked to your personal information will be kept by the study staff and never released to the agency. Therefore, the U.S. Food and Drug Administration will not be able to re-identify you. The U.S. Food and Drug Administration may share your coded information, as necessary, with the U.S. Food and Drug Administration affiliates who work within the scope of this consent; Advarra IRB and Regulatory agencies such as the National Health Authorities, and the European Medicines Agency.

You should be aware that some countries may not offer the same level of privacy protection as you are used to in the country where you live or where this study is conducted. However, the U.S. Food and Drug Administration will keep any information it receives to the same standard of confidentiality as far as permitted by applicable local law. The U.S. Food and Drug Administration has also entered into agreements with third parties working for the U.S. Food and Drug Administration to secure adequate protection of your data and samples.

The study information will be kept confidential within the limits of the law. The U.S. Food and Drug Administration may keep study samples and data collected for future research. Identifiers will be removed from your identifiable private information or identifiable biospecimens collected during this study so that data cannot be linked to you. The coded data and/or biospecimen could then be used for future research studies or distributed to another investigator for future research studies without additional informed consent. You will not be contacted about each of these future uses for additional informed consent. No additional participation time or procedures will be required beyond what is described above for the primary study. The coded data from the study will be replaced with a unique identifier and may be released to a data warehouse (location that will store the data) or used as part of a publication. It may be shared broadly for research purposes outside of the U.S. Food and Drug Administration and Spaulding Clinical Research, LLC. Other study doctors will have access to limited clinical and biological data such as age, gender, and disease status. Your samples will only be used for research purposes. It is also possible that your samples and data will never be used. Results of research done on your samples and data will not be available to your personal doctor. If the results of this study are published or presented in a meeting, you will not be named, and nobody will be able to tell that you were in the study from the publication or presentation.

WHOM TO CONTACT ABOUT THIS STUDY?

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research subject;

- Eligibility to participate in the study;
- The study doctor's or study site's decision to withdraw you from participation;
- Results of tests and/or procedures;

Please contact the study doctor at the telephone number listed on the first page of this consent document.

IF YOU SEEK EMERGENCY CARE, OR HOSPITALIZATION IS REQUIRED, ALERT THE TREATING PHYSICIAN THAT YOU ARE PARTICIPATING IN THIS RESEARCH STUDY.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, contact:

- By **mail**:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00076109.

An IRB is a group of people who review research studies to protect the rights and welfare of research subjects.

IS YOUR PARTICIPATION VOLUNTARY?

Yes, your participation in this study is strictly voluntary. You may refuse to take part in it, or you may stop participating at any time, even after signing this informed consent. There will be no penalty or loss of benefits to which you are otherwise entitled. However, if you decide to leave the study before it ends, the study doctor will need to see you before you are released from the study.

The study doctor may also decide to remove you from the study at any time without your consent. The study doctor may choose to take you out of the study because of unexpected or serious side effects, or for other scientific, technical, or safety considerations.

Examples of why you may be taken out of the study are:

- Staying in the study would be harmful
- You need treatment not allowed in this study
- You failed to follow instructions
- You become pregnant
- The study is cancelled
- Your study treatment arm is stopped

If your participation ends for any reason, you will return to the study for the following study procedures:

- Physical examination.
- Pregnancy test (if necessary)
- Body weight and body temperature
- Blood pressure and pulse rate
- ECG
- Blood draws for hematology and chemistry
- Blood draws for PK

- Urine will be collected for urinalysis
- Assessment for adverse events and concomitant medications (if you are taking any medications at the same time you were participating in the study)

If you should decide to leave the study, you should tell the study doctor or study staff. They will make sure that proper procedures are followed, and a final visit is made for your safety.

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

STATEMENT OF CONSENT

I have read this form, and its contents were explained to me. I agree to be in this research study for the purposes listed above and I agree to the genetic testing . All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

I agree to have photograph(s) to document adverse event(s) as applicable for this study. By signing this consent, I authorize the study doctor or study staff to take such a picture and provide it to the sponsor.

_____ ____/____/____

Signature of Research Subject Date

_____ _____

Printed Name of Research Subject Time (24hr)

STATEMENT OF PERSON OBTAINING INFORMED CONSENT

I have carefully explained to the subject the nature and purpose of the above study. There has been an opportunity for the subject to ask questions about this research study. I have been available to answer any questions that the subject has about this study.

_____ ____/____/____

Initials of Person Obtaining Informed Consent Date

HIPAA Authorization Agreement
Permission to Review, Use and Release Information about You

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study visits, including all test results.

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- Representatives of the U.S. Food and Drug Administration. (such as FDA representatives who may audit the research or receive reports of adverse events)
- Representatives of Spaulding Clinical Research, LLC.
- Representatives of Advarra IRB. (an Institutional Review Board that reviews this study)
- Other U.S. governmental agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STIs) must be reported.
- Governmental agencies of other countries.
- Labs working with the sponsor on this study.
- Other authorized users.

The U.S. Food and Drug Administration and those working for the U.S. Food and Drug Administration may use the coded health data sent to them:

- To see if the study drugs works and are safe.
- To compare the study drug to other drugs.
- For other research activities related to the study drug.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy laws.

Your permission to use and share health data about you will not end unless required by state law. If state law applies, your permission to use and share health data about you will end on December 31, 2060.

You may take back your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data. If you decide not to sign this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ____/____/____

Signature of Research Subject Date

_____

Printed Name of Research Subject

STATEMENT OF PERSON OBTAINING AUTHORIZATION

I have carefully explained to the subject the nature and purpose of this form. I have been available to answer any questions that the subject has about this form.

_____ ____/____/____

Initials of Person Obtaining Authorization Date