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

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CLINICAL STUDY PROTOCOL

Clinical Study to Evaluate Cannabidiol Liver Enzyme Elevations and Drug Interactions

PROTOCOL NO. SCR-016

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Version of Protocol: 3.0

Date of Protocol: March 19, 2024

CONFIDENTIAL

SPONSOR SIGNATURE PAGE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- International Council for Harmonisation (ICH) harmonised tripartite guideline E6 (R2): Good Clinical Practice; and
- All applicable laws and regulations, including without limitation, data privacy laws and compliance with appropriate regulations, including human subject research requirements set forth by the Institutional Review Board (IRB).

DocuSigned by:
David Strauss
Signer Name: David Strauss
Signing Reason: I approve this document
Signing Time: 21-Mar-2024 | 9:56:31 AM PDT
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21-Mar-2024

David Strauss, MD, PhD
U.S. Food and Drug Administration

Date

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol, the investigator brochure, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- ICH harmonised tripartite guideline E6 (R2): Good Clinical Practice;
- All applicable laws and regulations, including without limitation data privacy laws and regulations;
- Human subject research requirements set forth by the IRB;
- Regulatory requirements for reporting of serious adverse events (SAEs) defined in Section of this protocol; and
- Terms outlined in the Clinical Study Site Agreement.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Section 6 of this protocol.

DocuSigned by:
Melanie Fein
Signer Name: Melanie Fein
Signing Reason: I approve this document
Signing Time: 21-Mar-2024 | 12:49:59 PM CDT
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21-Mar-2024

Melanie Fein, MD
Principal Investigator

Date

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PROTOCOL SYNOPSIS

Protocol Number: SCR-016

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

Investigators: Melanie Fein, MD

Study Phase: 1

Study Period: This is a 2-part study. The duration of study participation will be up to 36 days (excluding the screening period) for Part 1. The duration of study participation will be up to 24 days (excluding the screening period) for Part 2.

Study Site: Spaulding Clinical Research Unit, West Bend, Wisconsin

Background and Motivation:

The cannabis plant contains bioactive compounds known as cannabinoids; delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most prevalent cannabinoids in most varieties of cannabis.[1] The Agricultural Improvement Act (Farm Bill) of 2018 removed hemp, defined as cannabis and derivatives of cannabis with extremely low concentrations of THC, from the definition of marijuana in the Controlled Substances Act.[1] Following this, many CBD products have been made available to consumers. However, hemp products remain subject to regulation under the Federal Food Drug & Cosmetic Act, when applicable (e.g., as drugs, foods, dietary supplements, cosmetics, veterinary products) and the growing CBD products market raises various safety concerns, especially with long-term use.[1]

CBD is available as a prescription drug product for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.[2] At labeled doses up to 25 mg/kg/day, an increased risk of liver enzyme elevation and drug-induced liver injury has been observed.[2,3] However, only limited evaluations of the risk of liver enzyme elevation of daily, lower dose CBD use are available.[3,4] 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.[2,5] 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.[6-8] As such, additional high-quality clinical pharmacology studies are needed to further characterize CBD's safety profile.

This study will be divided into two parts.

In Part 1, 200 healthy subjects will be randomized to 5 mg/kg/day of CBD (150 subjects) or placebo (50 subjects) for 4 weeks with weekly laboratory assessments to characterize the

percentage of participants with liver enzyme elevation (primary endpoint) or meeting withdrawal criteria for potential drug-induced liver injury (secondary endpoint). Additional secondary endpoints include the change from baseline to after 4 weeks of daily CBD dosing for male reproductive (testosterone and inhibin B) and thyroid hormones (thyroid stimulating hormone [TSH], triiodothryronine [T3] and thryroxine [T4]) as secondary endpoints. Exploratory endpoints include additional characterization of liver findings and other blood biomarkers.

In Part 2, 40 healthy subjects will receive either oral citalopram (20 subjects) or morphine (20 subjects) at baseline and then again after receiving CBD 5 mg/kg/day to characterize the effect of daily cannabidiol use on the plasma concentration of citalopram and morphine. Citalopram was selected because it is a common prescription medication for depression and anxiety that is metabolized by CYP2C19 and CYP3A4,[9] which CBD inhibits.[5] Morphine was selected because it is a common opioid analgesic that is metabolized by UGT2B7,[10] which CBD inhibits.[5]

Objectives:

Part 1:

To characterize the effects of daily cannabidiol use at a dose within the range of what consumers are taking as unapproved cannabidiol products on liver enzyme elevations and endocrine measures.

Part 2:

To characterize the effects of daily cannabidiol use at a dose within the range of what consumers are taking as unapproved cannabidiol products on drug interactions.

Endpoints:

Part 1:

- **Primary Endpoint:**
    - Percentage of participants with an ALT (based on consensus criteria*) or AST liver enzyme elevation greater than three times the upper limit of normal (>3 × ULN)
- **Secondary Endpoints:**
    - Percentage of participants meeting withdrawal criteria for potential drug-induced liver injury (DILI)
    - Change from baseline in total testosterone and inhibin B in male participants after CBD administration compared to placebo

- Change from baseline in thyroid stimulating hormone (TSH), total T3, and free T4 after CBD administration compared to placebo

- **Exploratory Endpoints:**
  - Assessment of liver-related adverse events
  - Summary of CBD and metabolite pharmacokinetics
  - Proportion of subjects with abnormal laboratory (e.g., liver, endocrine) tests
  - Changes in additional laboratory and plasma proteome assessments

***Consensus criteria for ALT elevation:** ULN for ALT will be 33 U/L for males and 25 U/L for females

Part 2 (Drug Interactions):

- **Primary Endpoints:**
  - Comparison of the area under the plasma concentration-time curve (AUC) and C_{max} of citalopram when administered alone versus when co-administered with CBD after 7 days of CBD dosing
  - Comparison of the morphine AUC and C_{max} when administered alone versus when co-administered with the first dose of CBD and after 7 days of CBD dosing
- **Secondary Endpoints:**
  - Comparison of the AUC and C_{max} of morphine metabolites when administered alone versus when co-administered with CBD
- **Exploratory Endpoints:**
  - Additional PK parameters for citalopram, morphine, CBD, and metabolites, such as time of maximum concentration, half-life, apparent clearance, and apparent volume of distribution
  - PK parameters for CBD and metabolites

Study Design:

This is a two-part study. Part 1 is a randomized, double-blind, placebo-controlled, parallel study in 200 subjects (150 subjects receiving 5 mg/kg/day of CBD and 50 subjects receiving placebo). Part 2 is an open-label, sequential study in 40 subjects (two separate cohorts of 20 subjects).

In Part 1, subjects will report to the study site for screening from Days -28 to -2 and then will return to the site on Day -1 for check-in, baseline assessments, and randomization. Subjects will check out from the clinical site on Day 1 (1 night in-house stay) following dosing and study assessments. Subjects will receive CBD or placebo for 28 days and will return to the study clinic on Day 28 for a single in-house day with check-out on Day 29. Subjects will have 3 clinic visits in between the in-house stays. The clinical site will contact subjects daily to remind subjects regarding their requirements for drug administration. Subject will have a final follow-up on Day 35.

In the Part 2 citalopram drug-drug interaction (DDI) cohort, subjects will report to the study site for screening from Days -28 to -2 and then will return to the site on Day -1 for check-in and baseline assessments. Subjects will check-out from the clinical site on Day 6 (6 nights in-house stay) following dosing and study assessments. Subjects will return to the study clinic on Day 12 for another 6 nights in-house stay with check-out on Day 18. Subjects will have one follow-up visit after the second check-out (Day 24). Subjects will receive CBD for 12 days (Day 6 to 17) and citalopram on Day 1 and Day 13.

In the Part 2 morphine DDI cohort, subjects will report to the study site for screening from Days -28 to -2 and then will return to the site on Day -1 for check-in and baseline assessments. Subjects will check-out from the clinical site on Day 6 (6 nights in-house stay) following dosing and study assessments. Subjects will return to the study clinic on Day 10 for a 3 night in-house stay with check-out on Day 13. Subjects will receive CBD for 9 days (Day 4 to 12) and morphine on Day 1, Day 4, and Day 11. Subjects will have one follow-up visit after the second check-out (Day 19).

In both parts, the clinical site will contact the subjects daily on outpatient days to remind drug administration. Subjects will undergo assessments as described in the Study Summary and Schedule of Events (Appendix A: Schedule of Events Part 1 and Appendix B: Schedule of Events Part 2).

Subject Population:

Approximately 240 healthy subjects are planned for enrollment.

Recruitment materials (e.g., internet, radio, and print advertisements, social media posts) will be approved by the local Institutional Review Board (IRB, i.e., Advarra) before telephone screening. Subjects will be offered payment for Screening and participation in the study, but no special incentives are offered.

Study Drugs, Dosage, and Route of Administration:

- Cannabidiol (Epidiolex) oral solution will be administered to approximately 190 participants (150 in Part 1 and 40 in Part 2). Dosing is 5 mg/kg/day administered in divided doses twice daily (i.e. 2.5 mg/kg twice daily).
- Oral placebo solution (matching characteristics of cannabidiol solution). Placebo will be administered twice daily to approximately 50 participants in Part 1.
- DDI substrate drugs: oral morphine (15 mg) and oral citalopram (20 mg). Of the participants in Part 2, 20 will receive morphine and 20 will receive citalopram.

For Part 1, subjects will be administered CBD on Day 1 and provided with adequate drug for at-home dosing on Days 2 through 6 at check-out. At the clinic visit on Day 7, subjects will receive dosing for the day as well as at-home dosing for Days 8 through 13. This will be repeated for clinic visits on Day 14 (primary study drug to cover dosing on Days 15 through 20) and Day 21 (primary study drug to cover dosing on Days 22 through 27). Subjects will continue to receive CBD twice daily after returning for check-in on Day 28 (last dose in the evening of Day 28).

For Part 2, subjects in the citalopram cohort will be administered CBD on Day 6 and subjects in the morphine cohort will be administered CBD on Day 4. Both Part 2 cohorts will be provided with adequate drug for at-home dosing at check-out. Subjects will continue to receive CBD twice daily after returning for check-in on Day 12 (citalopram DDI cohort) and Day 10 (morphine DDI cohort). The total number of days of CBD dosing will be 12 for the citalopram cohort and 9 for the morphine cohort. Subjects will be administered the DDI substrate drug on Days 1 and 13 (citalopram DDI cohort) and Days 1, 4, and 11 (morphine DDI cohort).

Key Inclusion Criteria:

Subject is a healthy, non-smoking man or woman, 18 to 55 years of age, inclusive, who weighs at least 50 kg (110 lbs) and has a body mass index of 18.5 to 33.0 kg/m^2, inclusive, at Screening and check-in. Healthy to be defined as subject having no clinically significant findings from medical history, physical examination, 12–lead ECG, vital sign measurements, and clinical laboratory evaluations.

Key Exclusion Criteria:

Subjects will be excluded from this study if they have:

1) Abnormal liver labs at screening or check-in (Day-1), defined as any of the following (tests may be repeated once for confirmation at screening and check-in):
    a) Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × ULN. (The ULN for ALT will be 33 U/L for males and 25 U/L for females)

b) Total bilirubin (TBL) > ULN

c) International normalized ratio (INR) > 1.3

2) Use or intend to use any medications/products in the 14 days prior to check-in (Day -1), unless deemed acceptable by the investigator

For a more detailed listing of inclusion/exclusion criteria, refer to sections 4.2.1 and 4.2.2 of the protocol.

Sample Collection

Number of samples collected throughout the study can be found in the Schedule of Events (see Appendices A and B). Unscheduled pharmacokinetic and proteomics samples will be collected in subjects from Part 1 who discontinue due to liver enzyme elevation as part of monitoring.

Pharmacokinetic Assessments:

The pharmacokinetic blood samples (6 mL each) will be collected into tubes containing K2EDTA, inverted several times to mix the blood with the anticoagulant, and placed in an ice bath. Within 30 minutes of collection, the samples will be centrifuged for 10 minutes, at 3000 relative centrifugal force (RCF), at 4°C, by a study team member.

The plasma will be separated using a disposable plastic pipette and approximately half of the plasma will be transferred into duplicate cryotube vials labeled as Aliquot A (primary) and Aliquot B (backup). The plasma samples will be appropriately labeled and stored frozen at –70°C or below within 30 minutes after aliquoting until shipment. Temperature monitoring logs should be maintained and accessible for review by the study monitor.

The Aliquot A samples (primary) will be shipped first, on dry ice, to the bioanalytical laboratory at FDA for processing when requested by the sponsor. The Aliquot B samples (backup) will be held for a second shipment after completion of all Aliquot A sample shipment(s) and the timing of the Aliquot B shipment will be communicated by the sponsor. Pharmacokinetic blood samples will be collected by direct venipuncture or by inserting an intravenous (IV) catheter on the following days.

For Part 1, a single blood sample will be collected on days 1, 7, 14, 21, 29, and 35. Total number of PK blood samples will be 6 per subject for Part 1.

For the Part 2 (citalopram DDI cohort), 13 PK samples will be obtained with each citalopram dose. Total number of PK blood samples will be 26 per subject for Part 2 (citalopram cohort).

For the Part 2 (morphine DDI cohort), 13 PK samples will be obtained with each morphine dose. Total number of PK blood samples will be 39 per subject for Part 2 (morphine cohort).

For detailed timing of PK sampling, refer to 4.7.1.1 Pharmacokinetic Sample Collection.

Additional Laboratory Assessments (Part 1):

For Part 1, blood samples for assessment of changes from baseline in different endocrine, lipids, and plasma proteins will be collected on Day 1 (morning, prior to dosing) and at check-out on Day 29 (morning, time-matched to the initial pre-dose assessment).

Blood samples will be collected by direct venipuncture or by inserting an intravenous (IV) catheter. Using red top tubes (no additives), approximately 8-10 mL of blood will be collected and processed for analysis. Additional details for sample collection and sample processing are in Section 4.7.2 to 4.7.4.

Safety Assessments:

Safety will be evaluated in terms of adverse events (AEs), clinical laboratory results (hematology, serum chemistry, and urinalysis), vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12-lead ECG, and physical examination findings.

Sample Size Determination:

Approximately 190 healthy participants planned for enrollment will be administered CBD. For Part 1, the primary endpoint is the percentage of CBD administered participants with an ALT (based on consensus criteria[*]) or AST liver enzyme elevation greater than three times the ULN. Assuming the true event rate is 6%, the study has 95% probability of observing 5 or more events with ALT or AST liver enzyme elevation greater than three times the ULN. Assuming the true observed drug-induced liver injury (DILI) event rate is 2%, the study has a 93% percent probability of observing 1 or more event.

In Part 1, change from baseline comparisons will be performed for various endocrine measures (e.g., total testosterone, inhibin B, TSH, total T3, and free T4). Sample size for the study is not powered for any of these comparisons nor are any adjustments planned for multiplicity.

In Part 2, comparisons will be performed on changes in exposure for two different substrate drugs following administration with CBD. Assuming no more than 20% discontinuations per arm, 30% intra-subject variability, and a two-sided test at the 0.05 significance level, the sample size would have 90% power to detect a 30% increase in exposure when the substrate drugs are co-administered with CBD.

Statistical Methods:

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics. Demographic and baseline characteristics will be summarized overall and by treatment for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized.

Descriptive statistics will be used to summarize demographic and baseline subject characteristics. For continuous variables, the mean, median, standard deviation (SD), minimum, and maximum values will be reported. For categorical (nominal) variables, the number and percentage of subjects (or observations) will be reported.

Primary Analysis (Part 1):

The primary endpoint is the percentage of subjects with an ALT (based on consensus criteria) or AST liver enzyme elevation greater than three times the upper limit of normal (ULN). Results will be reported as percentage with a 95% confidence interval (CI).

Secondary and Exploratory Analysis (Part 1):

The secondary liver endpoint is the percentage of participants with drug-induced liver injury (as defined by international consensus criteria). Analysis and reporting will be performed similar to the primary endpoint. Exploratory liver endpoints include the percentage of participants with ALT or AST above different thresholds. Additional liver analysis details will be specified in the Statistical Analysis Plan (SAP).

Endocrine endpoints will include the changes from baseline in serum total testosterone and inhibin B in males after CBD administration compared to placebo. Change from baseline in thyroid stimulating hormone, total T3, and free T4 in both males and females after CBD administration compared to placebo will also be assessed.

The percentage of subjects with either abnormal testosterone (males only) or abnormal laboratory tests will also be reported. Results will be presented as point estimates with associated 95% CI.

Additional details for secondary and exploratory analyses will be specified in the Statistical Analysis Plan (SAP).

Primary Analysis (Part 2):

The primary analysis for Part 2 will be a comparison of the area under the plasma concentration-time curve (AUC) and C_{max} of citalopram or morphine when administered alone versus when co-administered with CBD (for morphine, this will include with the first dose of

CBD and after 7 days of CBD dosing). Additional details will be specified in the Statistical Analysis Plan (SAP).

Secondary and Exploratory Analysis (Part 2):

For the secondary PK endpoints, AUC and C_{max} for morphine metabolites (alone and when co-administered with CBD) will be analyzed using the same approach as the primary PK endpoints.

Additional exploratory PK parameters for citalopram, morphine, CBD, and metabolites, such as time of maximum concentration, half-life, apparent clearance, and apparent volume of distribution will be analyzed using noncompartmental methods based on actual sampling times. All parameters will be calculated using statistical software. Mean and individual concentration time profiles will be presented in graphs.

Additional details will be specified in the Statistical Analysis Plan (SAP).

Safety (Part 1 and Part 2):

The safety population will include all subjects who receive at least 1 dose of the study drug. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs, organized by system organ class and preferred term, will be summarized with a focus on treatment-emergent AEs. Vital sign measurements will be summarized using descriptive statistics by time point. All values will be evaluated for clinically notable results. Data for additional safety parameters (e.g., physical examination findings) will be listed.

Date of Protocol:	J March 19, 2024

1. INTRODUCTION

The cannabis plant contains bioactive compounds known as cannabinoids; delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most prevalent cannabinoids in most varieties of cannabis.[1] The Agricultural Improvement Act (Farm Bill) of 2018 removed hemp, defined as cannabis and derivatives of cannabis with extremely low concentrations of THC, from the definition of marijuana in the Controlled Substances Act.[1] Following this, many CBD products have been made available to consumers. However, hemp products remain subject to regulation under the Federal Food Drug & Cosmetic Act, when applicable (e.g., as drugs, foods, dietary supplements, cosmetics, veterinary products) and the growing CBD products market raises various safety concerns, especially with long-term use.[1]

Cannabidiol (CBD) is extracted from Cannabis sativa L. plants. Pure CBD typically contains less than 0.1% (w/w) tetrahydrocannabinol (THC). CBD is available as a prescription drug product for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.[2] At labeled doses up to 25 mg/kg/day, an increased risk of liver enzyme elevation has been observed.[2,3] However, only limited evaluations of the risk of liver enzyme elevation of daily, lower dose CBD use are available.[3,4] 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.[2,5] 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.[6-8] As such, additional high-quality clinical pharmacology studies are needed to further characterize CBD's safety profile.

This study will be divided into two parts.

In Part 1, 200 healthy subjects will be randomized to 5 mg/kg/day of CBD (150 subjects) or placebo (50 subjects) for 4 weeks with weekly laboratory assessments to characterize the percentage of participants with liver enzyme elevation (primary endpoint) or meeting withdrawal criteria for potential drug-induced liver injury (secondary endpoint). Additional secondary endpoints include the change from baseline to after 4 weeks of daily CBD dosing for male reproductive (testosterone and inhibin B) and thyroid hormones (thyroid stimulating hormone [TSH], triiodothryronine [T3] and thryroxine [T4]) as secondary endpoints. Exploratory endpoints include additional characterization of liver findings and other blood biomarkers.

In Part 2, 40 healthy subjects will receive either oral citalopram (20 subjects) or morphine (20 subjects) at baseline and then again after receiving CBD 5 mg/kg/day to characterize the effect of daily cannabidiol use on the plasma concentration of citalopram and morphine. Citalopram was selected because it is a common prescription medication for depression and anxiety that is metabolized by CYP2C19 and CYP3A4,[9] which CBD inhibits.[5] Morphine was selected because it is a common opioid analgesic that is metabolized by UGT2B7,[10] which CBD inhibits.[5]

2. STUDY OBJECTIVES

Part 1:

To characterize the effects of daily cannabidiol use at a dose within the range of what consumers are taking as unapproved cannabidiol products on liver enzyme elevations and endocrine measures.

Part 2:

To characterize the effects of daily cannabidiol use at a dose within the range of what consumers are taking as unapproved cannabidiol products on drug interactions.

3. ENDPOINTS

3.1 Part 1

Primary Endpoint:

- Liver: Percentage of participants with an ALT (based on consensus criteria*) or AST liver enzyme elevation greater than three times the upper limit of normal (> 3 × ULN)

Secondary Endpoint:

- Percentage of participants meeting withdrawal criteria for potential drug-induced liver injury (DILI)
- Change from baseline in total testosterone and inhibin B in male participants after CBD administration compared to placebo
- Change from baseline in thyroid stimulating hormone (TSH), total T3, and free T4 after CBD administration compared to placebo

Exploratory Endpoints:

- Assessment of liver-related adverse events
- Summary of CBD and metabolite pharmacokinetics
- Proportion of subjects with abnormal laboratory (e.g., liver, endocrine) tests
- Changes in additional laboratory and plasma proteome assessments

***Consensus criteria for ALT elevation:** ULN for ALT will be 33 U/L for males and 25 U/L for females

3.2 Part 2 (Drug-Drug Interactions)

Primary Endpoints:

- Comparison of the area under the plasma concentration-time curve (AUC) and C_{max} of citalopram when administered alone versus when co-administered with CBD after 7 days of CBD dosing
- Comparison of the morphine AUC and C_{max} when administered alone versus when co-administered with the first dose of CBD and after 7 days of CBD dosing

Secondary Endpoints:

- Comparison of the AUC and C_{max} of morphine metabolites when administered alone versus when co-administered with CBD

Exploratory Endpoints:

- Additional PK parameters for citalopram, morphine, and metabolites, such as time of maximum concentration, half-life, apparent clearance, and apparent volume of distribution
- PK parameters for CBD and metabolites

4. INVESTIGATIONAL PLAN

4.1 Study Design

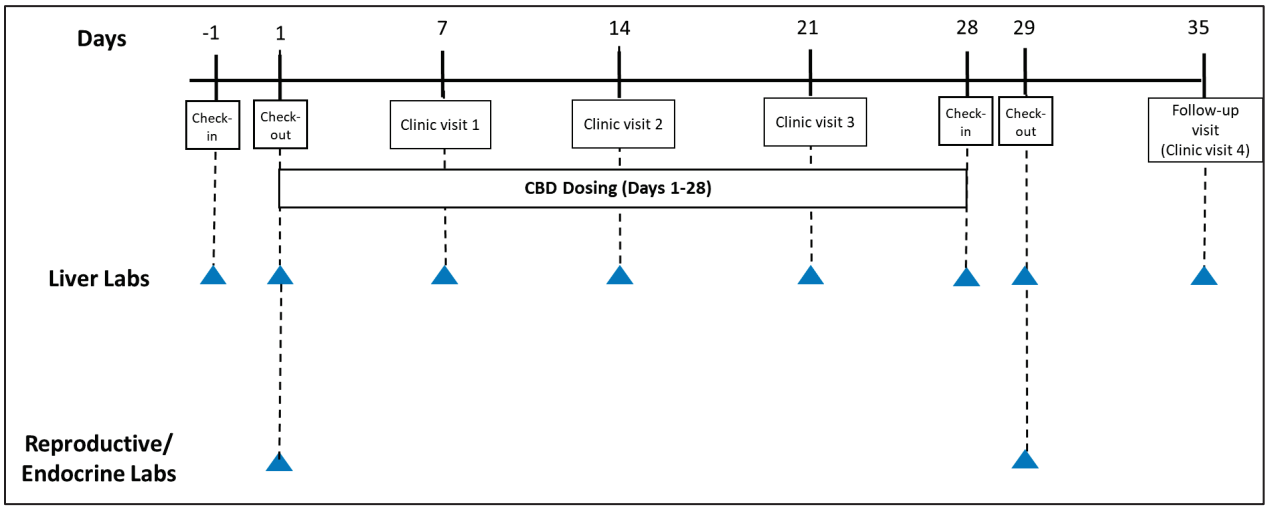
Part 1

Part 1 is a randomized, double-blind, placebo-controlled, parallel study in 200 subjects over a single treatment period of 28 days. Oral solution CBD at a dosage of 2.5 mg/kg twice a day, for a total of 5 mg/kg CBD daily, will be administered to the treatment group of 150 subjects. The placebo control group will consist of 50 subjects. Subjects will report to the study site for screening from Days -28 to -2 and then will return to the site on Day -1 for check-in and baseline assessments. Subjects will check-out from the clinical site on Day 1 (1-night in-house stay) following dosing and study assessments. Subjects will receive take-home doses of CBD or placebo for 28 days and will return to the study clinic on Day 28 for a single in-house day with check-out on Day 29. Subjects will have 3 clinic visits in between the in-house stays. The clinical site will have daily follow-ups with subjects during out-patient days to remind subjects regarding their requirements for drug administration. Subjects will have one follow-up visit on Day 35. Chemistry and hematology assessments will be performed on days -1, 1, 7, 14, 21, 28, 29, and 35. Endocrine assessments will be performed on days 1 and 29.

The study design is as follows:

	CBD Dosing Days 1-28 (5mg/kg/day)		

Day -1	Day 1	Day 7	Day 14	Day 21	Day 28	Day 29	Day 35
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

Part 2 is an open-label, sequential study in 40 subjects. This part will consist of two treatment cohorts, a citalopram DDI cohort and a morphine DDI cohort. Each treatment cohort will consist of 20 subjects.

In the citalopram DDI cohort, subjects will report to the study site for screening from Days -28 to -2 and then will return to the site on Day -1 for check-in and baseline assessments. Subjects will check-out from the clinical site on Day 6 (6 nights in-house stay) following dosing and study assessments. Subjects will return to the study clinic on Day 12 for another 6 nights in-house stay with check-out on Day 18. Subjects will have one follow-up visit after the second check-out (Day 24). Subjects will receive CBD for 12 days (Day 6 to 17) and citalopram on Day 1 and Day 13.

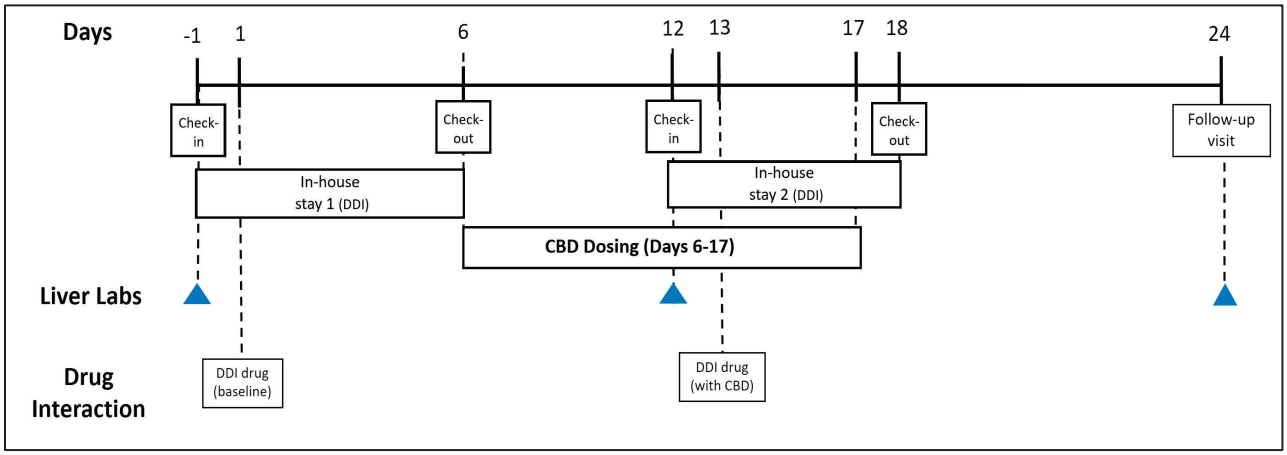
In the morphine DDI cohort, subjects will report to the study site for screening from Days -28 to -2 and then will return to the site on Day -1 for check-in and baseline assessments. Subjects will check-out from the clinical site on Day 6 (6 nights in-house stay) following dosing and study assessments. Subjects will return to the study clinic on Day 10 for a 3 night in-house stay with check-out on Day 13. Subjects will receive CBD for 9 days (Day 4 to 12) and morphine on Day 1, Day 4, and Day 11. Subjects will have one follow-up visit after the second check-out (Day 19).

In both parts, the clinical site will have daily follow-ups after the first check-out visit subjects return for the second check-in visit to remind drug administration.

The study design is as follows:

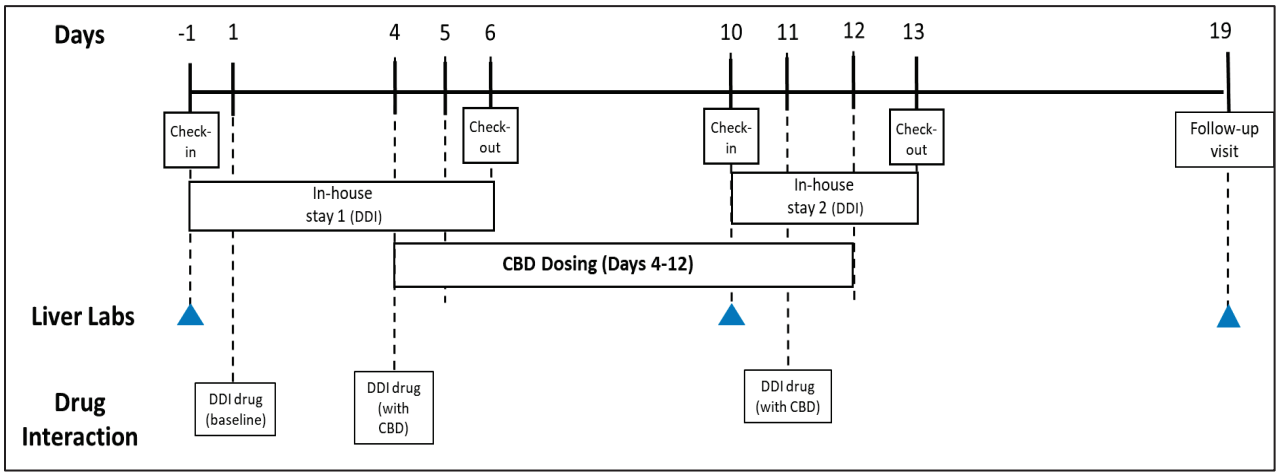
Citalopram DDI cohort

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



Parts 1 and 2

During the screening visit (Days -28 to -2 for both Part 1 and Part 2), the inclusion and exclusion criteria will be reviewed to ensure the subject is appropriate for the study. The informed consent form will be reviewed with the subject by a member of the study team and the subject will be encouraged to ask questions to ensure he or she has a good understanding of the study. If the subject is eligible and agrees to participate, the subject will be asked to sign the informed consent form before any study-specific procedure is performed, including randomization.

After the consent process is complete, demographic data, medical history, and concomitant medications will be recorded. A physical examination will be performed by a study team member. Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be performed. Female subjects must have a negative pregnancy test result. Screening tests will be performed within 28 days of and no later than 1 day before Day –1 for both parts. Subjects will undergo assessments as described above and in the Study Summary and Schedule of Events (Appendix A & B).

Subjects will be discharged from the study after completion of all study procedures. If a subject discontinues from the study prematurely, all procedures scheduled for the end of the study will be performed. Meal timing and components, activity levels, and general conditions in the study clinic will be as similar as possible on the treatment days. Subjects previously screened, but not initially enrolled in a cohort will be allowed to rescreen.

4.1.1. Risk/Benefit

Subjects will be informed that participation in a human clinical pharmacology study like the present one cannot be of benefit to healthy volunteers. Nevertheless, the information from the physical examination, vital sign measurements, and laboratory test results may be shared with the subject's personal physician if this is the subject's choice. Subjects will be informed that it is also their choice to inform their personal physician that they are participating in this research study.

Subjects will be informed that their contribution to the study is of major importance to agencies like the FDA to understand the effects of CBD on liver safety, endocrine measures, and drug-drug interactions. However, since this is a study involving healthy volunteers, subjects will be informed that they have the option not to participate.

Subjects will be informed that they may be exposed to risks associated with the pharmacological properties of the study drug and the study procedures. The following summary of potential AEs for the study drugs will be provided to and discussed with the subjects.

1. Oral cannabidiol 5 mg/kg/day: The most common adverse events include somnolence, decreased appetite, diarrhea, ALT/AST elevation, fatigue, malaise, asthenia, rash, insomnia/sleep disorder, and infection.[2]

2. Oral citalopram 20 mg: The most common adverse events include fever, arthralgia, myalgia, anorexia, agitation, somnolence, insomnia, sinusitis, ejaculation disorder (primarily ejaculatory delay), decreased libido, and impotence.[11]

3. Oral morphine 15 mg: The most common adverse events include constipation, nausea, sleepiness, lightheadedness, dizziness, drowsiness, vomiting, and sweating.[12]

Selected doses of individual drugs are within the FDA approved labeled doses.

- Cannabidiol – Cannabidiol (Epidiolex) will be administered orally 2.5 mg/kg BID for a total of 5 mg/kg/day for 28 days in Part 1 and for 9 days (morphine cohort) or 12 days (citalopram cohort) in Part 2. Labeled dosing initiates treatment at 5 mg/kg/day. Dosing is capped at 25 mg/kg/day for maximum maintenance dosage. DDI interactions can occur with drugs that are strong inducers/inhibitors of CYP3A4 or CYP2C19 and substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19. Studies with cannabidiol have initiated dosing at up to 25 mg/kg/day for 26 weeks[13], which is higher dosing and for a longer duration than proposed for this study.

- Citalopram – Citalopram (Celexa) will be administered once at 20 mg on days 1 and 13. Citalopram's initial dosage is 20 mg once daily with or without food and may increase to a maximum of 40 mg once daily.[11] DDI interaction included CYP2C19 inhibitor. The maximum recommended dose of citalopram is 20 mg/day for patients who are taking concomitant CYP2C19 inhibitor since it may lead to increased blood levels of citalopram and risk of QT prolongation or Torsade de Pointes.[14]

- Morphine – Morphine will be administered once at 15 mg on days 1, 4, and 11, which is within the range of labeled dosing. The initial dosage of morphine sulfate tablet is 15-30 mg every 4 hours as needed, but due to the risk of addiction, abuse, and misuse with opioids, it is recommended to use the lowest effective dosage for the shortest duration.[12]

The study drugs will not be administered to anyone who is pregnant. All women must take a pregnancy test before receiving any study drug in this study. All women of childbearing potential enrolled on this study will be informed that they must use effective birth control methods

(abstinence, intrauterine device, and contraceptive foam and a condom [i.e., double-barrier method]) during treatment. Subjects will be informed that they must notify the investigator if they or their female partners become pregnant during the study. If a subject becomes pregnant, she will be informed that neither Spaulding Clinical Research nor the sponsor will be responsible for the cost of any obstetric or related care, or for the child's care. Female subjects will also be informed of the importance of not becoming pregnant for 30 days following last medication dose. Male subjects will be informed of the importance of not fathering a child or donating sperm for 3 months following the last dose.

Subjects will be informed that insertion of an IV catheter may be required for blood sample collection and, during insertion of the catheter, soreness, bruising, or infection at the insertion site are possible but unlikely. Subjects will also be informed that dizziness and lightheadedness may occur during direct venipuncture, insertion of the IV catheter, or during blood collection.

Subjects will be informed that the confidentiality of their data will be respected at all times according to state law, and the study personnel handling their study data are bound by confidentiality agreements.

Subjects will be informed that they may eat only meals and snacks that are provided during periods of their stay in the study clinic, and that they must consume each meal that is served at a reasonable pace (within 25 minutes).

Subjects will be informed that extra precautions will be put in place, including required screening tests, that will limit the risk of COVID-19. Precautions will be documented in a COVID-19 risk management plan. Subjects will be informed that despite the extra precautions there is still a risk of them contracting COVID-19. Any changes to the COVID-19 precautions (e.g., due to updated CDC recommendations or new testing becoming available) will be documented in the COVID-19 risk mitigation plan.

Subjects will be informed that the study drug and all tests, procedures, and visits required by the study are provided at no cost to them. If subjects become ill or physically injured because of participation in this study, they will be informed that costs of treatment will not be covered by the sponsor.

4.2 Selection of Study Population

Subjects will be screened, and the data collected will be reviewed by the principal investigator. Only those subjects who meet all the eligibility criteria will be enrolled. Approximately 240 healthy subjects are planned for enrollment of which approximately 190 subjects will be administered CBD in parts 1 and 2. The DDI substrate drugs of oral morphine and oral citalopram will be used in part 2, with 20 subjects receiving morphine and 20 subjects receiving citalopram as per the schedule of events.

4.2.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria will be eligible to participate in the study:

1. Subject signs an IRB approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization) before any study related procedures are performed.

2. Subject is a healthy, non-smoking man or woman, 18 to 55 years of age, inclusive, who weighs at least 50 kg (110 lbs) and has a body mass index of 18.5 to 33.0 kg/m^2, inclusive, at Screening and check-in (Day -1).

3. Subject has normal medical history findings, clinical laboratory results, vital sign measurements, 12-lead ECG results, and physical examination findings at screening or, if abnormal, the abnormality is not considered clinically significant (as determined and documented by the investigator or designee).

4. Subject must have a negative test result for alcohol and illicit drugs at screening and check-in (Day -1).

5. Participants must agree to refrain from using any of the following for the duration of the study: alcohol, nicotine containing products, marijuana or marijuana-derived products, hemp or hemp-derived products, including CBD (except for provided study drug), and illicit drugs of any kind.

6. Subject must test negative for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) by a rapid antigen test at check-in for all study periods. If a subject's test comes back as invalid, the test can be repeated.

7. Female subjects must be of non-childbearing potential (non-childbearing potential includes post-menopausal females defined as spontaneous amenorrhea for at least 12 months with FSH in the post-menopausal range and females who have undergone a hysterectomy) or, if they are of childbearing potential, they must: 1) have negative serum HCG at screening and check-in 2) 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 application of study drug; OR 3) be practicing 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from Screening until at least 1 month after the end of the study.

8. Male subjects must agree to practice 2 highly effective methods of birth control (as determined by the investigator or designee) beginning at check-in (Day -1) until at least 3 months after the last dose of study drug. Male subjects may not donate sperm for 90 days after the end of the study.

9. Subject agrees to and is highly likely (as determined by the investigator) to comply with the protocol defined procedures and to complete the study.

4.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Abnormal liver labs at screening on check-in (Day –1), defined as any of the following (tests may be repeated once for confirmation at screening and check-in):
    a. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × ULN. (The ULN for ALT will be 33 U/L for males and 25 U/L for females.)
    b. Total bilirubin (TBL) > ULN.
    c. International normalized ratio (INR) > 1.3
2. Use or intend to use any medications/products in the 14 days prior to check-in (Day -1), unless deemed acceptable by the investigator
3. Subject is currently participating in another clinical study of an investigational drug or has been treated with any investigational drug within 30 days or 5 half-lives (whichever is longer) of dosing for this study.
4. Subject has used nicotine-containing products (e.g., cigarettes, cigars, chewing tobacco, snuff, electronic cigarettes) within 6 weeks of Screening. Subjects must refrain from using these throughout the study.
5. Subject has consumed alcohol, xanthine-containing products (e.g., tea, coffee, chocolate, cola), caffeine, kava melatonin, St Johns Wart, grapefruit, or grapefruit juice within 24 hours of check-in. Subjects must refrain from ingesting these throughout the study.
6. Subject is unable to tolerate a controlled, quiet study conduct environment, including avoidance of music, television, movies, games, and activities that may cause excitement, emotional tension, or arousal during the prespecified time points (e.g., before and during CBD dosing).
7. Subject has a history of consuming more than 14 units of alcoholic beverages per week within 6 months before Screening, has a history of alcoholism or drug/chemical/substance abuse within 2 years before Screening (Note: 1 unit = 12 ounces of beer, 4 ounces of wine, or 1 ounce of spirits/hard liquor).
8. Subject has a positive test result for alcohol or drugs of misuse (amphetamines, barbiturates, benzodiazepines, cocaine, alcohol, opiates, phencyclidine, propoxyphene, and methadone) at Screening or Check-in (Day -1 [both Parts]; Day 10 [morphine DDI]; Day 12 [citalopram DDI]). Subject has a positive test result for cannabinoids (THC) at screening or Day -1.
9. Subject has a history of opioid or narcotic misuse.
10. Subject has a history of suicidal ideation or previous suicide attempts

11. Subject has a history or evidence of a clinically significant disorder, condition, or disease (e.g., cancer, human immunodeficiency virus [HIV], hepatic or renal impairment) that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

12. Subject has a diagnosis of COVID-19 or any signs or symptoms that are consistent with COVID-19 per CDC recommendations at screening or check-in (Day -1). These include subjects with fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, or other symptoms indicative of likely COVID-19 in the opinion of the investigator.

13. Subject has known or suspected allergies or sensitivities to the study drug or placebo components (e.g., sucralose, sesame).

14. Subjects with a documented hypersensitivity reaction to cannabidiol

15. Subjects with a documented medical history of clinical disorders related to mood, anxiety or panic, including diagnosed depression, generalized anxiety disorder or panic attacks.

16. Subject has any condition possibly affecting study drug absorption (e.g., gastrectomy, Crohn's disease, irritable bowel syndrome). Uncomplicated cholecystectomies and appendectomies may be included at the investigator's discretion.

17. Subject has clinical laboratory test results (hematology, serum chemistry and urinalysis) at Screening or Check-In that are outside the reference ranges provided by the clinical laboratory and considered clinically significant by the investigator. Tests may be repeated once for confirmation at both Screening and Check-In.

18. Subject has a positive test result at Screening for HIV 1 or 2 antibody, hepatitis C virus antibodies, or hepatitis B surface antigen.

19. Subject has a mean systolic blood pressure <85 or >145 mmHg or a mean diastolic blood pressure <45 or >95 mmHg at either Screening or Check-in. Blood pressure will be measured in triplicate after the subject has been resting in a supine position for a minimum of 5 minutes.

20. Subject is unable or unwilling to undergo multiple venipunctures for blood sample collection because of poor tolerability or is unlikely to complete the study due to poor venous access.

21. Female subject is currently pregnant or lactating or was within 3 months of the study.

22. Subject has had any significant blood loss, donated 1 unit (450 mL) of blood or more, or received a transfusion of any blood or blood products within 60 days, or donated plasma within 7 days before Check-in.

23. Subject has any other condition that precludes his or her participation in the study (as determined by the investigator).

4.3 Screening Failures

Subjects who sign and date the informed consent form but who fail to meet the inclusion and exclusion criteria are defined as screening failures. A screening log, which documents the subject initials and reason(s) for screening failure, will be maintained by the investigator for all screening failures. A copy of the log should be retained in the investigator's study files.

If a subject fails the screening process because of an abnormal laboratory result, they can receive a copy of the results upon request. The investigator will determine if follow-up for the abnormal laboratory result is needed and will encourage the subject to follow up with his or her personal physician as appropriate. All subjects will be informed as to the reason(s) they are excluded from study participation, even if follow-up is not required. If a subject fails the screening process because of a positive test result for human immunodeficiency virus or hepatitis, the positive result will be reported to local health authorities as required by law.

4.4 Termination of Study or Investigational Site

4.4.1 Criteria for Termination of the Study

The study will be completed as planned unless one of the following criteria is satisfied that requires early termination of the study.

- New information regarding the safety or efficacy of the study drug(s) that indicates a change in the known risk profile for the study drug(s), such that the risk is no longer acceptable for subjects participating in the study.
- One or more serious adverse events (SAEs) that are determined to be related to the study drug occur. SAEs are defined as events that result in death, are life-threatening, or require hospitalization.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objective or compromises subject safety.

4.4.2 Criteria for Termination of the Investigational Site

The study site may be terminated if the site (including the investigator) is found in significant violation of GCP, the protocol, the contractual agreement, or is unable to ensure adequate performance of the study.

In the event that the sponsor elects to terminate the study or the investigational site, a study-specific procedure for early termination will be provided by the sponsor; the procedure will be followed by the applicable investigational site during the course of termination.

4.5 Criteria for Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn by the investigator without the approval of the subject based on the investigator's clinical judgment. A subject is not required to provide a written request to withdraw from the study; however, a written request is required if a subject withdraws consent for his or her personal data to be used for study related purposes.

A subject may be discontinued for any of the following reasons:

- AE: The subject has experienced an AE that, in the opinion of the investigator, requires early termination. The appropriate electronic case report form (eCRF) must be completed for each AE. If a subject is discontinued from the study due to an AE, the investigator is required to follow up with the subject until the event resolves or becomes stable. If a subject dies during the study, the cause of death must be reported as a serious AE (SAE), with an outcome of death noted in the eCRF.
- Withdrawal Criteria for Potential Drug-Induced Liver Injury (DILI): laboratory results meeting any of the following criteria.
    - ALT or AST > 3 x ULN (ULN for ALT is 33 U/L for males and 25 U/L for females) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) OR
    - ALT elevation ≥ 5 × ULN (ULN for ALT is 33 U/L for males and 25 U/L for females) OR
    - ALP elevation ≥ 2 × ULN (with accompanying elevations of GGT in the absence of known bone pathology driving the rise in ALP level) OR
    - ALT elevation ≥ 3 × ULN and bilirubin concentration > 2 × ULN

When subject withdrawal occurs due to potential DILI, the study drug will be discontinued, and monitoring will still be continued to document subsequent liver test results and resolution of biochemical abnormalities. Wherever possible, the investigator should arrange for the subject to return to the clinical site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of laboratory results to confirm that the subject meets the trial discontinuation criteria as well as to obtain detailed history and to perform a physical examination. Subjects should be followed with frequent (every 24 to 48 hours) repeat clinical laboratory assessments and any other appropriate assessments until all abnormalities normalize (in the investigator's opinion) or return to the baseline state. The subject will be discontinued from the study and returned to the study site for repeat and follow-up assessments. These follow-up steps are outlined in more detail in a separate procedures document.

- Protocol Violation: The subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.
- Withdrawal by Subject: The subject (or other responsible individual [e.g., caregiver]) wishes to withdraw from the study in the absence of a medical need.

  NOTE: Withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.
- Study Terminated by Sponsor: The sponsor, IRB, FDA, or other regulatory agency terminates the study.
- Pregnancy: The subject is found to be pregnant.

  NOTE: If the subject is found to be pregnant, the subject must be withdrawn immediately. The pregnancy will be followed up to term, and the outcome, including any premature termination will be recorded. All live births must be followed for a minimum of 30 days or until the first well-baby visit.
- Other.

  NOTE: This category records withdrawals caused by an accidental or a medical emergency, unblinding, and other rare cases. The specific reason should be recorded in the comment space of the eCRF.

4.5.1 Handling of Withdrawals

The investigator may terminate a subject's study participation at any time during the study when the subject meets the criteria described in Section 4.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Subjects will be informed that their participation in the study is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Should a subject's participation be discontinued, the primary reason for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

4.5.2 Replacement of Subjects

Approximately 240 healthy subjects are planned for study enrollment with Part 1 having 150 subjects randomized to CBD dosing and 50 subjects to placebo control. Approximately 40 healthy subjects are planned for enrollment in Part 2 (20 subjects per DDI cohort). Replacement subjects may be assigned depending on discontinuations during Part 1 and 2.

4.6 Study Visits

4.6.1 Recruitment

Recruitment materials (e.g., internet, radio, and print advertisements, social media posts) will be approved by the local IRB before telephone screening. The sponsor is responsible for registration of the study on clinicaltrials.gov. Recruitment may not occur until the study is fully registered on clinicaltrials.gov.

4.6.2 Compensation

Subjects will be offered payment for Screening; however, if the results of their alcohol and drug screening tests are positive, they will not be compensated. Subjects who complete the entire study will receive payment according to the schedule provided in the informed consent form. No special incentives are offered. Final payment will not be released until all follow-up procedures have been completed and accepted by the investigator.

If a subject chooses to withdraw from the study prematurely, he or she will only be compensated for completed days. If subjects are withdrawn for medical reasons or if the study is halted temporarily or permanently, the subjects will receive compensation proportional to the time spent in the study. No compensation will be provided if a subject is dismissed from the study for noncompliance (e.g., improper conduct, ingesting alcohol and/or drugs [including recreational drugs], tampering with the study drug, consuming any prohibited foods or beverages).

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

4.6.3 Screening

The following procedures and assessments will be performed at Screening for both parts (Days -28 to –2):

- Obtain informed consent/HIPAA authorization. The informed consent process will be performed by a clinical research nurse in a private room. The subject will be given unlimited time to ask questions regarding study participation, and each subject will be questioned to ensure their understanding.

After informed consent is obtained:

- Review inclusion/exclusion criteria to confirm subject eligibility
- Record demographic information
- Measure height, weight, and calculate body mass index

- Perform serology screening (HIV antigen/antibody [Ag/Ab] Combo 1/2, HepC antibody, HBsAg)
- Record medical history
- Perform alcohol and drug screening (amphetamines, barbiturates, benzodiazepines, cocaine, alcohol, opiates, phencyclidine, propoxyphene, cannabinoids (THC), and methadone)
- Perform urine cotinine test
- Perform a serum pregnancy test (female subjects only)
- Perform FSH assessment (postmenopausal [i.e., spontaneous amenorrhea for at least 12 months] female subjects only)
- Record prior medications
- Monitor for AEs
- Perform clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Perform a safety 12 lead ECG
- Perform a complete physical examination

4.6.4 Study Periods

4.6.4.1 Check-In (Day -1)

The following procedures and assessments will be performed at check-in (Day -1 for both parts):

- Perform/review results from SARS-CoV-2 rapid antigen test
- Review inclusion/exclusion criteria to confirm subject eligibility
- Review medical history
- Perform targeted physical examination
- Weight measurement
- Perform alcohol and drug screening (amphetamines, barbiturates, benzodiazepines, cocaine, alcohol, opiates, phencyclidine, propoxyphene, cannabinoids (THC), and methadone)
- Perform liver function tests (ALT, AST, GGT, ALP, PT/INR, TBili)

- Perform urine cotinine test
- Perform a serum pregnancy test (female subjects only)
- Admit subject to the study clinic
- Randomization (after completion of check-in procedures or just before dosing on Day 1 of each study period) (Only Part 1)
- Record concomitant medications
- Monitor for AEs
- Perform clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Perform a safety 12 lead ECG

4.6.4.2 Treatment

The following procedures and assessments will be performed during the treatment period. Please refer to the Schedule of Events (Appendix A and B) for the specific days of assessments.

- Monitor for AEs
- Record concomitant medications
- Administer study drug according to Schedule of Events (Appendix A and B). Administration of study drug [Part 1: clinic visits and Day 28, Part 2: Day 12 (citalopram) and Day 10 (morphine)] can occur prior to review of safety labs.
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature).
- Perform targeted physical examination (at investigator's discretion)
- Collect PK blood samples (6 mL) at timepoints specified in Section 4.7.1.1. Blood samples will be collected by direct venipuncture or by inserting an intravenous (IV) catheter.
- Collect blood samples for laboratory tests.
- Collect whole blood sample for pharmacogenetic testing (Only Part 2)

4.6.4.3 Discharge (or Early Termination)

The following procedures and assessments will be performed before a participant is discharged at the end of the study or at early termination:

- Perform liver function tests (ALT, AST, GGT, ALP, PT/INR, TBili)
- Record concomitant medications
- Monitor for AEs
- Measure height, weight, and calculate body mass index
- Perform clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Perform a serum pregnancy test (female subjects only)
- Collect PK blood sample (6 mL)
- Perform a safety 12-lead ECG
- Perform a complete physical examination
- Discharge subject from the study clinic after completion of all study procedures

4.7 Study Procedures

4.7.1 Pharmacokinetic Assessments

4.7.1.1 Pharmacokinetic Sample Collection

Pharmacokinetic blood samples will be collected by direct venipuncture or by inserting an IV catheter. In Part 1, a single blood sample will be collected on Day 1, Day 7 (clinic visit), Day 14 (clinic visit), Day 21 (clinic visit), Day 29, and a final sample collection at follow-up on Day 35. Clinic visits may be completed outside of the listed visit day per investigator's decision. Total number of PK blood samples will be 6 per subject for Part 1. 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. All lab collections will take place predose and within 1 hour of mealtime.

Part 1 PK collections:

- Days 1, 7, 14, 21, 29, 35

For Part 2, both the citalopram and morphine DDI cohorts will have 13 PK samples obtained during each in-house stay. Total number of PK blood samples will be 26 per subject for the citalopram DDI cohort and 39 per subject for the morphine DDI cohort. 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.

Part 2 PK collections:

- Citalopram DDI cohort
  - 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
- Morphine cohort
  - 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

4.7.1.2 Pharmacokinetic Specimen Handling

The PK blood samples (6mL each) will be collected into tubes containing K_2EDTA, inverted several times to mix the blood with the anticoagulant, and placed in an ice bath. Within 30 minutes of collection, the samples will be centrifuged for 10 minutes, at 3000 RCF, at 4°C, by a study team member.

The plasma will be separated using a disposable plastic pipette and equally aliquoted into duplicate cryotube vials labeled as Aliquot A (primary) and Aliquot B (backup). The plasma samples will be appropriately labeled and stored frozen at -70°C or below within 30 minutes after aliquoting until shipment. Temperature monitoring logs should be maintained and accessible for review by the study monitor.

The Aliquot A samples (primary) will be shipped first, on dry ice, to the bioanalytical laboratory at FDA for processing when requested by the sponsor. The Aliquot B samples (backup) will be held for a second shipment after completion of all Aliquot A sample shipment(s) and the timing of the Aliquot B shipment will be communicated by the sponsor. None of the PK blood samples will be stored at the clinical facility for future use.

4.7.1.3 Pharmacokinetic Parameters

The following PK parameters will be determined for Part 2 which will include citalopram and morphine with or without CBD.

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration time curve (AUC)
- Time at which C_{max} occurs (T_{max})
- Elimination rate constant (K_{el})
- Terminal half-life ($t_{1/2}$)

4.7.2 Endocrine Assessments

Endocrine assessments will be collected in Part 1 on the study days outlined below to determine total testosterone and inhibin B for males, and thyroid panel with TSH values for all participants.

Blood samples will be collected by direct venipuncture or by inserting an intravenous (IV) catheter. Using red top tubes (no additives), approximately 8-10 mL of blood samples will be collected to provide sufficient serum for all scheduled assays—total testosterone, inhibin B, and thyroid function (TSH, total T3, free T4).

For Part 1, blood samples for endocrine assessment will be collected on Day 1 (morning, prior to dosing) and at check-out on Day 29 (morning, time-matched to the initial pre-dose assessment).

4.7.2 Lipid Assessments

For the lipid assessment, approximately 5 mL of whole blood will be collected and processed for serum. Blood samples will be collected by direct venipuncture or by inserting an intravenous (IV) catheter. Samples will be collected into red top tubes (no additives).

For Part 1, blood samples for lipid assessments will be collected on Day 1 (morning, prior to dosing) and at check-out on Day 29 (morning, time-matched to the initial pre-dose assessment). Lipid assessments will include total cholesterol, LDL, HDL, and triglycerides.

4.7.2 Proteomics Assessments

For the proteomics assessments, approximately 5 mL of whole-blood samples will be collected and processed for plasma. Whole blood should be collected in BD Vacutainer® Venous Blood Collection Tubes containing EDTA (or any other primary blood collection tube containing EDTA as anticoagulant) and stored at room temperature (15–25°C) or 4°C before processing within 1 hour. Heparin-containing blood collection tubes should not be used as this anticoagulant can interfere with downstream analyses.

Plasma samples should be processed, aliquoted (approximately 700 µL volumes), and placed into the -80C freezer within 2 hours of collection.

For Part 1, blood samples for proteomics assessments will be collected on Day 1 (morning, prior to dosing) and at check-out on Day 29 (morning, time-matched to the initial pre-dose assessment).

4.7.3 Safety Assessments

Safety will be evaluated in terms of AEs, clinical laboratory results (hematology, serum chemistry, and urinalysis), vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12 lead ECG results, and physical examination findings.

4.7.3.1 Adverse Events

4.7.3.1.1 Adverse Event Definitions

An AE is defined as any untoward and/or unintended sign, including an abnormal clinical laboratory finding, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Events or conditions that increase in frequency or severity during or as a consequence of use of a drug in human clinical trials will also be considered AEs.

A treatment emergent adverse event (TEAE) is defined as an AE that begins after study drug administration.

An unexpected AE is any AE having a specificity or severity not consistent with the current investigator's brochure for the study drug(s).

A serious adverse event (SAE) is defined as any AE occurring at any dose that meets the following criteria:

- Results in death,
- Is life threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Results in a congenital anomaly/birth defect due to exposure prior to conception or during pregnancy, or
- Is an important medical event that may not meet the previous criteria but, based upon appropriate medical judgment, jeopardizes the subject or requires medical or surgical intervention to prevent one of the outcomes listed previously.

4.7.3.1.2 Adverse Event Reporting

The recording of AEs will begin after the subject signs the informed consent form and will continue until discharge (or early termination). All AEs, whether serious or nonserious and whether or not related to the study drug, must be recorded in the eCRF. Study subjects will be instructed to warn study staff if he or she has any unexpected symptoms. In addition, all subjects will receive a reminder telephone call approximately 24 h before check-in.

Any SAE (whether expected or unexpected) must be entered into the eCRF system and reported by email to the medical monitor or designee using the SAE Reporting Form within 24 h of the investigator or study clinic staff becoming aware of the event. It is the responsibility of the investigator to report all SAEs to the medical monitor, to provide the most complete report possible, and to assess each SAE for its relationship to the study drug. The investigator is responsible for obtaining follow-up information on all SAEs and submitting follow-up SAE data. Any unexpected SAEs must be reported promptly to the investigator's IRB as per the IRB's requirements.

In the event of a fatal or life-threatening SAE, the sponsor will notify the appropriate FDA authorities within 7 calendar days of receipt of the report. The sponsor will follow all 7 day alert reports with a written report within 10 working days of receipt of the case. Serious AE cases that concern nonfatal, non-life-threatening events that are unexpected and at least possibly related to the study drug will be submitted in writing to the FDA within 10 working days of receipt.

Furthermore, any AEs that are not expected, occur at a higher frequency, or would require modification of the study protocol and/or informed consent must be reported to the FDA within 10 working days.

Adverse events that are assessed by the investigator as possibly or probably related to the study drug will be followed until they resolve or stabilize. All SAEs will be followed until resolution.

4.7.3.1.3 Assessment of Severity

The investigator will assess the severity of each AE using the following scale:

- Mild: The subject is aware of the AE but is still able to perform all activities; minimal or no medical intervention or therapy is required.
- Moderate: The subject has to discontinue some activities due to the AE; minimal or no medical intervention or therapy is required.
- Severe: The subject is incapacitated by the AE and is unable to perform normal activities; significant medical intervention or therapy is required, and hospitalization is possible.

4.7.3.1.4 Assessment of Causality

The investigator will assess the causal relationship/relatedness of each AE to the study drug using the following scale:

- Not Related: Onset of the AE has no reasonable temporal relationship to administration of the study drug, a causal relationship to administration of the study drug is biologically implausible, or the event is attributed to an alternative etiology.
- Unlikely Related: Onset of the AE has a reasonable temporal relationship to study drug administration and although a causal relationship is unlikely, it is biologically plausible.
- Possibly Related: Onset of the AE has a strong temporal relationship to administration of the study drug, cannot be explained by the subject's clinical state or other factors, and a causal relationship is biologically plausible.
- Probably Related: Onset of the AE shows a distinct temporal relationship to administration of the study drug that cannot be explained by the subject's clinical state or other factors, the AE is a known reaction to the product or chemical group or can be predicted by the product's pharmacology.

4.7.3.1.5 Pregnancy

A serum pregnancy test will be performed for female subjects at the time points presented in the Schedule of Events (Appendix A and B). If a subject becomes pregnant while on the study, this should be reported immediately to the investigator, the subject will be withdrawn from the study and the medical monitor and the subject will be instructed to follow up with his or her personal physician. All pregnancies are to be reported as an AE and followed for outcome.

4.7.3.2 Clinical Laboratory Tests

Clinical laboratory and diagnostic screening tests will be performed at the time points presented in the Schedule of Events and will be collected in accordance with acceptable laboratory procedures. Clinical laboratory testing will be performed by the clinical study contractor(s). The clinical laboratory tests that will be performed are presented in Table 4-1. Unused clinical laboratory test samples will not be stored for future use.

Table 4--1: Clinical Laboratory Tests & Diagnostic Screening Tests

Hematology	Serum Chemistry	Urinalysis
Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count (with automated differential)	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Bilirubin (total, direct, and indirect) Blood urea nitrogen Calcium Chloride Creatinine (including calculated creatinine clearance by CKD-EPI) Gamma-glutamyl transferase Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total protein Uric acid <u>Specific laboratory tests (Part 1):</u> Total and free testosterone Inhibin B Thyroid stimulating hormone Triiodothyronine (total T3) Thyroxine (free T4) Lipid Panel <u>Additional assessments in subjects for liver enzyme monitoring:</u> International normalized ratio (INR) Prothrombin time	Appearance Bilirubin Blood Color Glucose Ketones Leukocyte esterase Microscopic examination: red blood cells, white blood cells, epithelial cells, bacteria, crystals, and casts (if present) Nitrite pH Protein Specific gravity Urobilinogen
Diagnostic Screening Tests:		
Serum	**Urine**	**Whole Blood**
Serology (human immunodeficiency virus Ag/Ab Combo 1/2, hepatitis C virus antibody, and hepatitis B surface antigen) **Female Subjects Only** Human chorionic gonadotropin (for pregnancy) Follicle-stimulating hormone	Drug screen including amphetamines, barbiturates, benzodiazepines, cocaine, alcohol, cannabinoids (THC) (excluded for Day 28 check-in, Part 1), opiates, phencyclidine, propoxyphene, methadone, and cotinine	Pharmacogenetic testing may be performed (CYP2C19, Day-1 Part 2 citalopram cohort; UGT2B7, Day -1 and Part 2 morphine cohort). Additional details will be provided in a separate laboratory document.
Other		
SARS-CoV2 rapid antigen test		

Clinical laboratory results will be reviewed by the investigator or designee together with data in the eCRF. Any values outside the reference range will be evaluated for clinical significance. If a value is determined to be clinically significant, the subject will be instructed to follow up with his or her personal physician. The investigator or designee may repeat the clinical laboratory tests if deemed appropriate. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

4.7.3.2.1 Assessment and Reporting of Potential Cases of Drug-Induced Liver Injury

The investigational site is required to submit to the sponsor the laboratory results for any subject after admission to the study that meets one of the following criteria:

- ALT or AST > 3 x ULN (ULN for ALT is 33 U/L for males and 25 U/L for females) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

  OR

- ALT elevation ≥ 5 × ULN (ULN for ALT is 33 U/L for males and 25 U/L for females)

  OR

- ALP elevation ≥ 2 × ULN (with accompanying elevations of GGT in the absence of known bone pathology driving the rise in ALP level)

  OR

- ALT elevation ≥ 3 × ULN and bilirubin concentration > 2 × ULN

When subject withdrawal occurs due to potential Drug-Induced Liver Injury (DILI), the study drug will be discontinued, and monitoring will still be continued to document subsequent liver test results and resolution of biochemical abnormalities. Laboratory results meeting any one of the above criteria, along with a copy of baseline laboratory results, must be sent to the the sponsor within 24 hours of becoming aware of the results. Wherever possible, the investigator should arrange for the subject to return to the clinical site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of laboratory results to confirm that the subject meets the trial discontinuation criteria as well as to obtain detailed history and to perform a physical examination. Subjects should be followed with frequent (every 24 to 48 hours) repeat clinical laboratory assessment and any other appropriate assessments until all abnormalities normalize (in the investigator's opinion) or return to the baseline state. The subject will be discontinued from the study and returned to the study site for repeat and follow-up assessments. These follow-up steps are outlined in more detail in a separate procedures document.

In addition, the severity of all instances of DILI are to be assessed according to the International DILI Expert Working Group's severity index[15] (Appendix D). This severity assessment will occur in addition to the AE reporting procedures detailed in 4.7.3.1.2 (Adverse Event Reporting).

4.7.3.3 Vital Sign Measurements

Vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured using an automated device at the time points presented in the Schedule of Events (and B). Vital signs may be repeated at investigator discretion.

4.7.3.4 Safety 12-lead Electrocardiograms

12-lead ECGs will be obtained with the subjects in the supine position before recording. ECGs will be overread by a physician. If an abnormality is observed, the subject will be instructed to follow up with his or her personal physician.

4.7.3.5 Physical Examinations

A complete physical examination will be performed at the time points presented in the Schedule of Events (Appendix A and B).

The complete physical examination will include, but not be limited to, assessments of the head, eyes, ears, nose, throat, skin, thyroid, nervous system, respiratory system, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. Height, weight (without shoes and wearing the lightest possible clothing), and calculation of body mass index will be performed at Screening and check-out.

If a clinically significant abnormality is observed upon physical examination, the subject will be instructed to follow up with his or her personal physician.

4.7.4 Demographics and Medical History

Demographic data (date of birth, gender, race, and ethnicity) will be collected at Screening.

Each subject will provide a complete medical history at Screening that will be reviewed at check-in. Specific information relating to any prior or existing medical conditions/surgical procedures will be recorded in the subject's eCRF.

4.8 Study Treatments

4.8.1 Dose Selection and Rational

Cannabidiol (Epidiolex) oral solution will be obtained for 190 participants (150 in Part 1 and 40 in Part 2) to receive cannabidiol twice daily as per the Schedule of Events. All dosing will be oral. Anticipated dosing is 5 mg/kg/day administered in divided doses twice daily (i.e. 2.5 mg/kg twice daily). Oral placebo solution (matching characteristics of cannabidiol solution) will be obtained for 50 participants in Part 1 to receive placebo twice daily as per the schedule of events.

Cannabidiol's label indicates a maximum dosage of 20 mg/kg/day, therefore the proposed study dose of 5 mg/kg/day is lower than the maximum therapeutic dose noted in the label. Data from a recent meta-analysis marked 400 mg/day as an upper limit of what can be considered low dose CBD and attainable using over the counter CBD products.[16] In this study, total daily dosing will be in line with this threshold (200 mg twice daily for an 80 kg person). The anticipated DDI substrate drugs are oral morphine and oral citalopram. Of the participants in Part 2, 20 will receive morphine and 20 will receive citalopram as per the schedule of events.

4.8.2 Treatments Administered and Schedule

Study drugs for both parts will be administered by a clinical research nurse on the study clinic floor during check-ins and in-house stays. The pharmacist or investigator will be available if needed during study drug administration. Oral study drugs (Part 2) will be administered with 240 mL of room -temperature water. During study days not on site, subjects will be required to take the study drugs twice daily at home. A member of the study team will follow up daily with each subject to ensure compliance with dosing schedule. Because levels of CBD may be affected by food, subjects will be instructed to take CBD consistently with regards to meals. Subjects will be instructed to take CBD after eating breakfast and dinner during at-home days. During in-house stays, CBD will be given approximately 30 minutes after the start of breakfast and dinner. A fasting period of 4 hours will be required before all time points when clinical laboratory samples will be obtained. In addition, for Part 1, a fasting period of 8 hours will be required prior to lipid profile sampling on check-out Days 1 and 29.

For Part 1 and Part 2, each instance of primary study drug administration will consist of an identical volume of prepared study drug oral solution. Placebo solution will be used to match treatments when needed. A study drug diary, designed by the clinical site and approved by the local IRB, will be given to each subject to monitor study drug tolerance and patient outcomes.

4.8.2.1 Method of Assigning Subjects to Treatment Sequence

4.8.2.1.1 Randomization Process

The project biostatistician will create the specifications that will be used to generate the randomization schedule. The specifications will be based on the protocol requirements and appropriate statistical programming with consideration for study design, number of treatments, number of subjects planned for enrollment, stratification, and blocking.

Based on these specifications, the project biostatistician (or designee) will generate a dummy randomization schedule. The schedule is generated in R.

The project biostatistician (or designee) distributes the 'dummy' randomization schedule to specified personnel and pharmacy for review. Any change (e.g., change in block size, change in stratification levels) that requires an update to the specifications will reset this process. Minor changes (e.g., display formatting) will not require a change to the specifications.

After the approval of the 'dummy' randomization schedule, the project biostatistician (or designee) transfers the program used to generate the 'dummy' schedule to the randomization biostatistician (unblinded), who is an independent party and will not be participating in any programming or statistical decisions for the study before breaking the blind. No transfer is necessary if the unblinded randomization biostatistician also created the 'dummy' randomization.

The randomization biostatistician is responsible for generating the final randomization schedule. The output is sent only to designated unblinded recipients, who will maintain a secured digital and printed copy for their use.

Archival of the programs and output is accomplished by the creation of an encrypted, password-protected ZIP file containing the program and output file(s). The ZIP file is copied to a secure storage drive on the sponsor's site.

Randomization will occur after informed consent is obtained in Part 1, either after completion of check-in procedures on Day -1 or just before dosing on Day 1. Approximately 200 healthy male and female subjects are planned for enrollment in Part 1 (150 subject receiving CBD and 50 receiving placebo).

All randomization information will be secured and housed in a locked storage area, accessible only by the randomization personnel and the assigned pharmacist and his or her verifier.

4.8.2.1.2 Identity of Study Drugs

Cannabidiol (Epidiolex) is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex. It is extracted from Cannabis sativa L. plants. Cannabidiol (Epidiolex) is a clear, colorless to yellow liquid available in 100 mg/mL oral solution. The compound cannabidiol is a white to pale yellow crystalline solid, insoluble in water but soluble in organic solvents. Cannabidiol has a molecular weight of 314.46, and molecular formula is C21H30O2.[2]

Citalopram (Celexa) is a selective serotonin reuptake inhibitor (SSRI) indicated for treatment of major depressive disorder. Citalopram hydrobromide occurs as a fine, white to off-white powder, and sparingly soluble in water and ethanol. Citalopram (Celexa) is orally administrated tablet available as 10 mg, 20 mg, and 40 mg strength tablets contain 12.49 mg, 24.98 mg, and 49.96 mg of citalopram hydrobromide, respectively. Citalopram has a molecular weight of 405.35, and molecular formula is C20H22BrFN2O.[11]

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 for oral administration. Morphine sulfate USP is a white to off-white crystalline powder or a fine white to light yellow powder, it is soluble in water and slightly soluble in alcohol but is practically insoluble in chloroform or ether. Morphine sulfate has a molecular weight of 668.80, and molecular formula is C34H40N2O10S.[12]

Placebo solution will be supplied by the clinical site.

4.8.3 Management of Clinical Supplies

4.8.3.1 Study Drug Packaging and Storage

The active study drugs will be obtained from commercial sources. Storage instructions for the active study drugs are as follows:

- Cannabidiol solution should be stored at 20° to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F). Do not refrigerate or freeze. Use within 12 weeks of first opening the bottle, then discard any remainder.[2]
- Citalopram tablets should be stored at 25°C (77°F) with excursions permitted from 15° to 30°C (59° to 86°F).[11]
- Morphine tablets should be stored at 20° to 25°C (68° to 77°F) and protected from moisture.[12]

Placebo solution will be supplied by the clinical site and stored per USP requirements.

4.8.3.2 Study Drug Accountability

Good clinical documentation practices will be employed to record the receipt, storage conditions, accountability, and use or return of the study drug. The study drug will be stored in a secure location with access to the study personnel who will be managing the storage, dispensing, and accountability of the study drug.

Upon completion or termination of the study, final accountability review by the study monitor, and written authorization from the sponsor, all unused and/or partially used study drug should be returned or destroyed at the study clinic. It is the investigator's responsibility to ensure that the sponsor has provided written authorization for study drug disposal, the disposal process follows the study clinic's standard operating procedures, and appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the study monitor (or designee). Documentation of unused study drug should include subject number, medication identity (medication #, period #), date, and quantity of study drug used.

4.8.4 Blinding

Part 1 of the study will be double-blind, and the blind will be maintained through a randomization schedule held by the dispensing pharmacist. The pharmacist (and designated staff member responsible for confirmation of study drug dose) will be unblinded to subject treatment assignment; however, the pharmacist will not perform any study procedures other than study drug preparation and dispensing.

Additional details regarding blinding can be found in the Spaulding Blinding SOP which will be followed to ensure the blind is maintained throughout the study.

4.8.4.1 Breaking the Blind

The study drug blind will not be broken by the investigator or designee unless information concerning the study drug is necessary for the medical treatment of the subject. For unblinding a subject, the randomization information for unblinding can be obtained by contacting the dispensing pharmacist. The sponsor or medical monitor must be notified immediately if the study drug blind is broken. The date, time, and reason that the blind was broken will be recorded in the source documents. If the blind is broken by the investigator or designee, the study drug must be stopped immediately, and the subject must be withdrawn from the study. Data or specimens already collected from subjects who discontinue prematurely and for whom the blind is broken will be made available for analysis if needed.

4.8.5 Treatment Compliance

For in-house visits, all doses of the study drug will be administered in the study clinic either under direct observation of or administered by clinic personnel and recorded in the eCRF. If a subject vomits after dosing, the event will be documented as an AE. For outpatient days, subjects will be contacted daily by clinical site staff regarding dosing and reminded to consistently take the study drug approximately 30 minutes after the start of breakfast and dinner. For out-patient visits or second check-in days, an inventory of study drug consumed and study drug remaining will be completed.

4.8.6 Prior and Concomitant Medications

Subjects are prohibited from using any prescription or nonprescription drugs (including aspirin or NSAIDs and excluding contraceptives) within 14 days or 5 half-lives (whichever is longer), or complementary and alternative medicines within 28 days before the first dose of study drug. This includes prescription or nonprescription ophthalmic drugs. Note the only drugs permitted are contraceptives. Subjects will be asked if they have used any of medication and their responses will be recorded on the eCRF.

Subjects are also prohibited from currently participating in another clinical study of an investigational drug and may not have been treated with any investigational drug within 30 days or 5 half-lives (whichever is longer) of the compound.

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. During the study, low dose acetaminophen or ibuprofen may be allowed with investigator's approval for minor symptoms.

4.8.7 Subject Restrictions

Subjects are not allowed to use nicotine containing products (e.g., cigarettes, cigars, chewing tobacco, snuff, electronic cigarettes) within 6 weeks before Screening. In addition, subjects are

not allowed to ingest alcohol, xanthine containing products (e.g., tea, coffee, chocolate, cola), caffeine, kava melatonin, St Johns Wart, grapefruit, or grapefruit juice within 24 h of check-in of all study periods. Subject must refrain from ingesting alcohol, xanthine containing products (e.g., tea, coffee, chocolate, cola), caffeine, kava melatonin, St Johns Wart, grapefruit, or grapefruit juice throughout the entire study. Subjects are not allowed to use aspirin or NSAIDs within 14 days before the first dose of study drug. Subjects will be asked if they have used any of these substances and their responses will be recorded on the eCRF.

Subjects must be able to tolerate a controlled, quiet study conduct environment, including avoidance of music, television, movies, games, and activities that may cause excitement, emotional tension, or arousal during prespecified times throughout the duration of the study.

Subjects must be willing to comply with study rules; attempting to void at specified times; remaining quiet, awake, undistracted, motionless, and supine during specified times; and avoiding vigorous exercise as directed throughout the duration of the study.

A fasting period of at least 4 hours will be required before all time points when clinical laboratory samples will be obtained. In Part 1, all subjects will fast overnight for a minimum of 8 hours (no food or fluid except water) before blood collection for lipid testing on check-out days 1 and 29. Standardized meals will be served at consistent times relative to dosing for in-house days, and no food or fluids will be served containing caffeine. Outside of mealtimes, the subjects will only be allowed to intake water, which will be available ad libitum. 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 (e.g., study drug administration or eating) when instructed by 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.

Designated isolation rooms will be set up to segregate any participant(s) that develop any symptoms of concern while housed in the unit and COVID-19 testing will be done when deemed necessary by the Investigator. If new information becomes available, there could be other precautions that lead to additional restrictions that will be documented in the COVID-19 Risk Management Plan and/or the study specific COVID-19 Procedure Plan.

4.9 Statistical Methods

4.9.1 Sample Size

A total of 240 healthy subjects are planned for enrollment and approximately 190 of these will be administered CBD. The primary endpoint is the percentage of CBD administered participants with an ALT (based on consensus criteria*) or AST liver enzyme elevation greater than three times the ULN. Assuming the true event rate is 6%, the study has 95% probability of observing 5 or more events with ALT or AST liver enzyme elevation greater than three times the ULN. Assuming the true observed drug-induced liver injury event rate is 2%, the study has a 93% percent probability of observing 1 or more event.

In Part 1, change from baseline comparisons will be performed for various endocrine laboratory measures (e.g., total testosterone, inhibin B, TSH, total T3, and free T4). Sample size for the study is not powered for any of these comparisons nor are any adjustments planned for multiplicity.

In Part 2, comparisons will be performed on changes in exposure for two different substrate drugs following administration with CBD. Assuming no more than 20% discontinuations per arm, 30% intra-subject variability, and a two-sided test at the 0.05 significance level, the sample size would have 90% power to detect a 30% difference in exposure when the substrate drugs are co-administered with CBD.

4.9.2 Analysis Populations

Part 1

The liver safety analysis population will include all subjects who receive at least 1 dose of any of the study drugs and have liver lab data (ALT and AST) for the treatment period collected before dosing and at 1 or more time points after dosing. The liver safety analysis population will be used for all liver safety analyses.

The laboratory analysis population will include subjects that have laboratory/proteomics measures (e.g., free and total testosterone, inhibin B, TSH, total T3, free T4, lipid panel, proteomics) from pre-dose on Day 1 and check-out on Day 29 (time-matched to Day 1). The laboratory population will be used for all analyses involving change from baseline in laboratory/proteomics measures.

The safety population will include all subjects who receive at least 1 dose of the study drug.

Part 2

The PK population will include all subjects who receive the study drug and have at least 1 estimable PK parameter after dosing with the substrate drug alone and with the substrate drug in combination with CBD.

The safety population will include all subjects who receive at least 1 dose of the study drug.

4.9.3 General Statistical Considerations

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics. Demographic and baseline characteristics will be summarized overall and by treatment for all subjects.

4.9.4 Subject Disposition

The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized.

4.9.5 Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline subject characteristics. For continuous variables, the mean, median, standard deviation (SD), minimum, and maximum values will be reported. For categorical (nominal) variables, the number and percentage of subjects (or observations) will be reported.

4.9.6 Primary and Secondary Analyses

Part 1

The primary endpoint is the percentage of subjects with an ALT (based on consensus criteria) or AST liver enzyme elevation greater than three times the upper limit of normal (ULN). Results will be reported as percentage with a 95% confidence interval. The secondary liver endpoint is the percentage of participants meeting withdrawal criteria for potential drug-induced liver injury. Analysis and reporting will be performed similar to the primary endpoint.

Secondary endpoints involving laboratory measures will include the changes from baseline in serum total testosterone and inhibin B in males after CBD administration compared to placebo. Change from baseline in thyroid stimulating hormone, total T3, and free T4 in both males and females after CBD administration compared to placebo will also be assessed. These analyses will use a mixed-effect analysis approach. The model will include treatment as fixed effects and subject as a random effect. Testing will be two-sided, and a significant increase will be concluded if the two-sided 95% CI excludes 0. In addition, the percentage of subjects with either abnormal total testosterone (males only) or abnormal laboratory tests will also be reported. Results will be presented as point estimates with associated 95% CI.

Part 2

The primary analysis for Part 2 will be a comparison of the area under the plasma concentration-time curve (AUC) and C_{max} of citalopram or morphine when administered alone versus when co-administered with CBD (for morphine, this will include after co-administration with CBD for 1-day and 7-days). The PK parameters (AUC and C_{max}) will be analyzed using noncompartmental methods based on actual sampling times. Using linear mixed-effects modeling, comparisons of

log-transformed PK parameters will be performed. Treatment will be a fixed effect. Subject will be included as a random effect on the intercept. Treatment differences on the log-scale will be estimated for the PK parameters. Geometric mean ratio and 90% CI will be obtained by exponentiation of the treatment effect and 90% CI based on the log-transformed scale.

For the secondary PK endpoints, AUC and C_{max} for morphine metabolites (alone and when co-administered with CBD) will be analyzed using the same approach as the primary PK endpoints.

4.9.6.1 Additional Analyses

Part 1

Assessment of liver-related adverse events will be performed consistent with FDA's Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation. This will include but is not limited to the following categorical and visual summaries:

- 3x-, 5x-, 10x-, and 20x ULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated TBL to >2x ULN.
- Any elevations of ALP >1.5xULN.
- Elevation of ALT or AST (>3x ULN) accompanied by elevated bilirubin (>1.5x ULN, >2x ULN).
- Elevation of ALT or AST in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue.

Portions of collected blood samples from this study will be used for evaluating laboratory measures and differentially expressed plasma proteins. Additional details regarding the methods for the exploratory analyses will be described in a separate protocol. Steady state CBD and metabolite drug concentrations will be summarized by visit using descriptive statistics.

Part 2

Additional exploratory PK parameters for citalopram, morphine, CBD, and metabolites, such as time of maximum concentration, half-life, apparent clearance, and apparent volume of distribution will be analyzed using noncompartmental methods based on actual sampling times. All parameters will be calculated using statistical software. Mean and individual concentration time profiles will be presented in graphs.

4.9.10 Safety Analyses

4.9.10.1 Adverse Events

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. The incidence of TEAEs, organized by system organ class and frequency, will be

summarized by seriousness, severity, relationship to treatment, and by treatment at onset of the TEAE. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

4.9.10.2 Clinical Laboratory Tests

Clinical laboratory results will be reviewed by the investigator or designee together with data in the eCRF. Any values outside the reference range will be evaluated for clinical significance. If a value is determined to be clinically significant, the subject will be instructed to follow up with his or her personal physician. The investigator or designee may repeat the clinical laboratory tests if deemed appropriate. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

4.9.10.3 Vital Sign Measurements

Vital sign measurements and changes from baseline will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) by treatment and time points as specified in Section 4.7.3.3.

4.9.10.4 Safety 12-lead Electrocardiograms

12-lead ECGs will be obtained with the subjects in the supine position for a minimum of 10 minutes before recording. ECGs will be overread by a physician or other trained clinical team staff. If an abnormality is observed, the subject will be instructed to follow up with his or her personal physician.

4.9.10.5 Physical Examinations

Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

4.9.10.6 Other Safety Data

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

4.9.11 Interim Analyses

No interim analyses are planned.

4.9.12 Missing Data

Missing data will not be imputed. Data that are excluded from the descriptive or inferential analyses will be included in the subject data listings. This will include data from subjects not in the particular analysis population, measurements from unscheduled visits, or extra measurements that may arise from 2 or more analyses of the biofluid sample at the same time point. Details on the handling of missing data will be further described in the Statistical Analysis Plan (SAP).

4.10 Data Quality Assurance

Completed eCRFs are required for each subject randomly assigned to treatment. Electronic data entry will be accomplished through the ClinSpark® remote electronic data capture system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

4.11 Data Sharing

De-identified subject-level data may be released to other researchers (including through a data warehouse or as a part of a publication) to enable secondary research. Additional secondary research may also be performed by the sponsor.

5. ETHICAL CONSIDERATIONS

5.1 Ethical Conduct of the Study

This study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964 and later revisions, as well as United States Title 45 Code of Federal Regulations (CFR) Part 46 GCP, and International Council for Harmonisation (ICH) guidelines describing technical requirements for registration of pharmaceuticals for human use.

5.2 Institutional Review Board (IRB)

The FDA Project Lead or investigator will provide the designated IRB with all required documents, including the study protocol and informed consent form. The study will not be initiated until appropriate IRB approval is obtained from the designated IRB. The investigator

will provide the FDA Project Lead with copies of the approval documents for the protocol, informed consent form, and all recruiting materials. The designated IRB will also receive copies of any original or amended information sheets or pamphlets given to the study subject in support of the informed consent process and any advertisements or other recruitment material. Such materials will not be employed in the study before approval by the designated IRB.

Subjects will be informed that they have the right to contact the IRB or Office for Human Research Protections if they have any questions, concerns, complaints, or believe they have been harmed by the participation in this research study as a result of investigator negligence. Subjects will be given the address and phone number of the IRB.

6. ADMINISTRATIVE PROCEDURES

6.1 Responsibilities of the Investigator

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes may be reported to the IRB but will not result in protocol amendments.

6.1.1 Form FDA 1572

The investigator will complete and sign the Form FDA 1572.

6.1.2 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with the ICH E6(R2) and all applicable guidelines and regulations.

6.1.3 Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit reports to the IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

6.1.4 Source Documentation

By participating in this study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories.

6.1.5 Retention of Records

The investigator agrees to keep the records stipulated in this protocol and those documents that include (but are not limited to) the study-specific documents, identification log of all

participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent form), copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities, the sponsor, or its designees.

Furthermore, ICH 4.9.5 requires the investigator to retain essential documents specified in Section 8 of ICH E6(R2) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

6.1.6 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 45 CFR 46. In addition, the investigator must provide to the sponsor a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor the study clinic is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process.

6.2 Confidentiality and Disclosure of Data

All subjects will sign a HIPAA compliant authorization form containing the mandated core elements and requirements before participation in this clinical study. The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's electronic data capture system database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes such as gender, age or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires that the investigator allow review of the subject's original medical records (source data or documents) by the study monitor, representatives from any regulatory authority (e.g., FDA), the sponsor's designated auditors, and the appropriate IRB. These medical records will include, but will not be limited to, clinical laboratory test result reports, ECG reports,

admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the sponsor must have personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected in the subject's eCRF).

Data will be maintained and backed up in the electronic data capture system. All access to the data is protected by username and password, and each staff member and all sponsor staff will have separate access that requires a separate username and password. Access is only given to site staff and requested sponsor staff who have completed the appropriate training.

6.3 Subject Consent

Written informed consent in compliance with 45 CFR 46 will be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to the study clinic. If any institution-specific modifications to study related procedures are proposed or made by the study clinic, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to the IRB for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all active participating subjects must sign the revised form.

Before enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved informed consent form. The informed consent process will be performed by a clinical research nurse in a private room. The subject will be given unlimited time to ask questions regarding study participation, and each subject will be questioned to ensure their understanding. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the informed consent form.

The investigator will provide a copy of the signed informed consent form to the subject. The original form will be maintained in the subject's medical records at the site.

6.4 Data Collection

Full details of procedures for data collection and handling will be documented in the data management plan, which is initiated with the final protocol receipt. The data management plan is a changing document that evolves over the course of the study and is finalized by database lock.

6.5 Publications

No information related to or generated by this study will be released to the public until it has been reviewed by the sponsor. The sponsor shall own intellectual rights for the data and analysis

resulting from this study. Authorship on publications will be determined by standard journal requirements.

7. STUDY MANAGEMENT

7.1 Monitoring

The sponsor or its designee will monitor the study to ensure that it is being conducted according to the protocol, GCP standards, and applicable region-specific requirements, and to ensure that study initiation, conduct, and closure are adequate. The investigators and the study clinic staff will be expected to cooperate fully with the study monitors and personnel or agents of the sponsor and be available during monitoring visits to answer questions sufficiently and to provide any missing information. The investigators and their institutions will permit direct access to source data/documents for study related monitoring activities, audits, IRB reviews, and regulatory inspections.

During any on-site visits, the study monitor will:

- Check and assess the progress of the study
- Review all informed consent forms
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution
- Verify that the facility remains acceptable
- Conduct study drug accountability

These monitoring activities will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- The safety and rights of the subjects are being protected.
- The study is being conducted in accordance with the currently approved protocol (including any amendments), GCP, and all applicable regulatory requirements.

In addition, the sponsor, designated auditors, and government inspectors must be allowed access to eCRFs, source documents, and other study files that may be required to evaluate the conduct of the study.

7.2 Management of Protocol Amendments and Deviations

7.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be submitted to the sponsor or designee and reviewed and approved by the local IRB before implementation. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before subjects are enrolled into an amended protocol.

7.2.2 Protocol Violations and Deviations

Any significant protocol deviations that the investigator or study clinic staff believes are of major importance (e.g., incorrect randomizations, subject enrolled but not eligible) should be reported to the sponsor and the investigator's IRB as soon as possible. Significant protocol deviations may include the following:

- Deviations from the inclusion/exclusion criteria that may affect subject safety
- Deviations (omission or delay) of safety monitoring procedures
- Deviations in the administration of the study drug
- Deviations in obtaining informed consent

All subjects who are enrolled and receive the study drug, regardless of whether they have a major protocol violation, must continue to be followed for safety for all follow-up study visits.

Reference list

1. U.S. Food and Drug Administration (FDA) Science Board. (2022, June 3). Background materials for the June 14, 2022 meeting of the Science Board to the FDA. Retrieved from https://www.fda.gov/advisory-committees/advisory-committee-roster/science-board-fda/2022-meetings#event-materials.
2. Cannabidiol (Epidiolex ®) oral solution label obtained from https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
3. Lo, LA, Christiansen, A, Eadie, L, Strickland, JC, Kim, DD, Boivin, M, et al. Cannabidiol-associated hepatotoxicity: A systematic review and meta-analysis. J Intern Med. 2023; 293: 724–752.
4. Crippa JAS, Zuardi AW, Guimarães FS, et al. Efficacy and Safety of Cannabidiol Plus Standard Care vs Standard Care Alone for the Treatment of Emotional Exhaustion and Burnout Among Frontline Health Care Workers During the COVID-19 Pandemic: A Randomized Clinical Trial. JAMA Netw Open. 2021;4(8):e2120603. doi:10.1001/jamanetworkopen.2021.20603
5. U.S. Food and Drug Administration (FDA). Clinical Pharmacology and Biopharmaceutics Review. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000ClinPharmR.pdf
6. EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck, D, Bohn, T, Castenmiller, J, De Henauw, S, Hirsch-Ernst, KI, Maciuk, A, Mangelsdorf, I, McArdle, HJ, Naska, A, Pelaez, C, Pentieva, K, Siani, A, Thies, F, Tsabouri, S, Vinceti, M, Cubadda, F, Frenzel, T, Heinonen, M, Marchelli, R, Neuhäuser-Berthold, M, Poulsen, M, Prieto Maradona, M, Schlatter, JR, Trezza, V, van Loveren, H, Albert, O, Dumas, C, Germini, A, Gelbmann, W, Kass, G, Kouloura, E, Noriega Fernandez, E, Rossi, A and Knutsen, HK, 2022. Statement on safety of cannabidiol as a novel food: data gaps and uncertainties. EFSA Journal 2022; 20(6):7322, 25 pp. https://doi.org/10.2903/j.efsa.2022.7322
7. Carvalho, RK, Andersen, ML, Mazaro-Costa, R. The effects of cannabidiol on male reproductive system: A literature review. J Appl Toxicol. 2020; 40: 132–150. https://doi.org/10.1002/jat.3831
8. Tallon, MJ, Child, R. Subchronic oral toxicity assessment of a cannabis extract. Regulatory Toxicology and Pharmacology. 2023; 144. https://doi.org/10.1016/j.yrtph.2023.105496.
9. Anderson, LL, Doohan, PT, Oldfield, L, Kevin, RC, Arnold, JC, Berger, M, Amminger, PG, McGregor, IS. Citalopram and Cannabidiol: In Vitro and In Vivo Evidence of Pharmacokinetic Interactions Relevant to the Treatment of Anxiety Disorders in Young

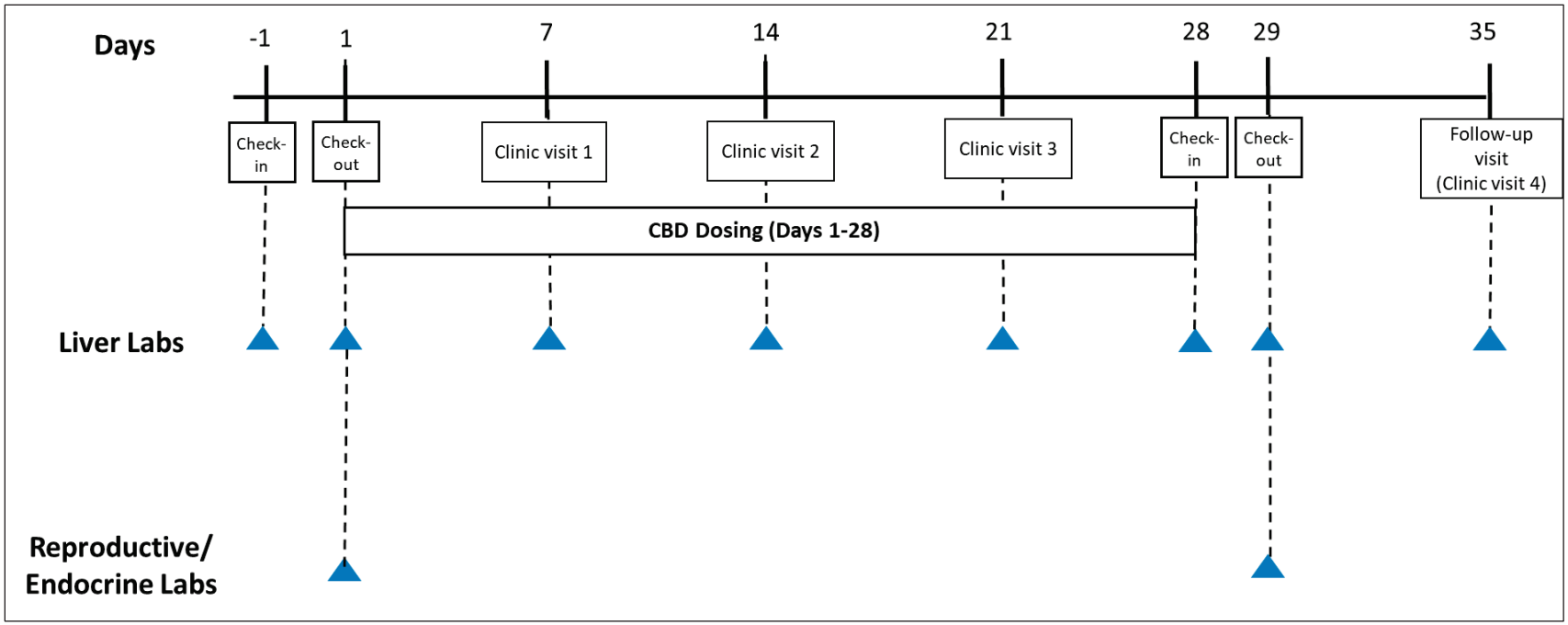
People. Journal of Clinical Psychopharmacology. 41(5):p 525-533, DOI: 10.1097/JCP.0000000000001427

10. Armstrong, SC, Cozza, KL. Pharmacokinetic Drug Interactions of Morphine, Codeine, and Their Derivatives: Theory and Clinical Reality, Part I. Psychosomatics. 2003, 44:2:167-171. https://doi.org/10.1176/appi.psy.44.2.167.
11. Citalopram (Celexa ®) tablet label obtained from https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020822s041lbl.pdf
12. Morphine Sulfate tablet label obtained from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022207s010lbl.pdf
13. Iannone LF, Arena G, Battaglia D. Results From an Italian Expanded Access Program on Cannabidiol Treatment in Highly Refractory Dravet Syndrome and Lennox-Gastaut Syndrome. Front Neurol. 2021 May 20;12:673135. doi: 10.3389/fneur.2021.673135.
14. Sharbaf Shoar N, Fariba KA, Padhy RK. Citalopram. StatPearls https://www.ncbi.nlm.nih.gov/books/NBK482222/
15. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, Wilke RA, Avigan M, Kaplowitz N, Bjornsson E, Daly AK. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011 Jun;89(6):806-15. doi: 10.1038/clpt.2011.58. Epub 2011 May 4. PMID: 21544079.
16. Arnold JC, McCartney D, Suraev A, McGregor IS. The safety and efficacy of low oral doses of cannabidiol: An evaluation of the evidence. Clin Transl Sci. 2023 Jan;16(1):10-30. doi: 10.1111/cts.13425. Epub 2022 Oct 19. PMID: 36259271

8. APPENDICES

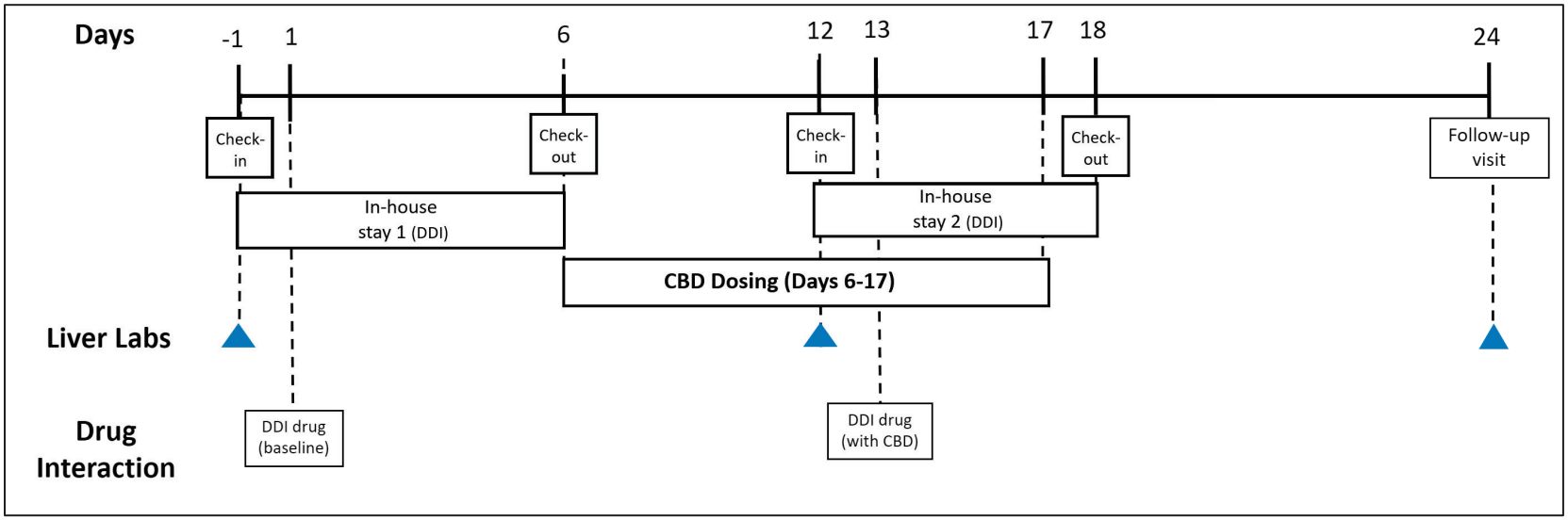
Appendix A – Schedule of Events – Part 1

	Screening	Check-in	Treament Period																												Check-out	Follow-up
			Check-out						clinic visit 1							clinic visit 2							clinic visit 3							Check-in		
Study Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	35
Clinic Visits									1							2							3									4
In House Residency		X																												X		
Meals		X																												X		
Informed Consent	X																															
Medical History	X	X																														
Comprehensive Physical Exam	X																															X
Targeted Physical exam		X	X						X							X							X							X	X	
Vital signs	X	X	X						X							X							X							X	X	X
Height/Weight	X	X																														X
ECG - single	X	X																														X
Urinalysis	X	X																														X
Urine cotinine test	X	X																														
Urine drug screen + alcohol screen	X	X																												X		
Pregnancy test (females only)	X	X																														X
FSH (females only)	X																															
COVID19 Test		X																												X		
HIV test	X																															
Hepatitis test	X																															
CBD Dosing (oral)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PK Samples			1						1							1							1								1	1
Serum Chemistry, Hematology, and Liver function tests (ALT, AST, GGT, ALP, PT/INR, Tbili)	X	X	X						X							X							X							X	X	X
Thyroid Panel (TSH, Total T3, Free T4); Total and free testosterone, Inhibin B			X																												X	
Lipid Panel/Profile (Total cholesterol, LDL, HDL, Triglycerides)			X																												X	
Proteomics			X																												X	
Con Med/AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eSource Management		X																														


Days
-1
1
7
14
21
28
29
35
Check-in
Check-out
Clinic visit 1
Clinic visit 2
Clinic visit 3
Check-in
Check-out
Follow-up visit (Clinic visit 4)
CBD Dosing (Days 1-28)
Liver Labs
Reproductive/ Endocrine Labs

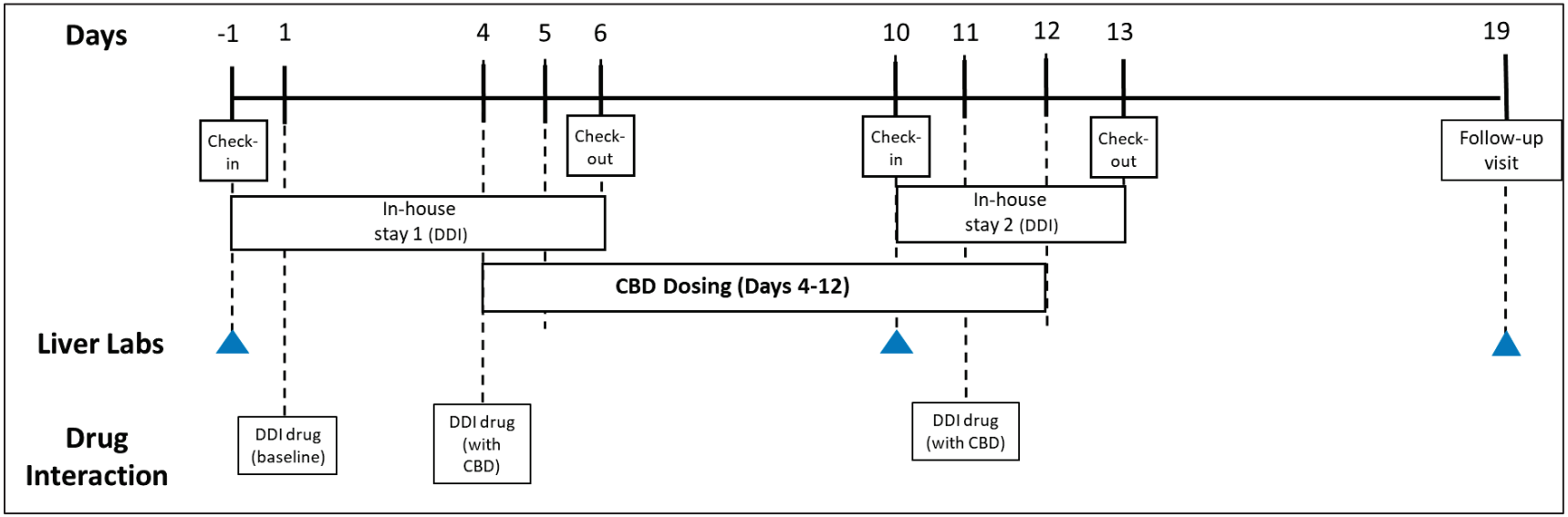
Appendix B – Schedule of Events – Part 2.1 (Citalopram)

	Screening	Check-in	Treatment Period																	Check-out	Follow-up
								Check-out						Check-in							
Study Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	24
In House Residency		X	X	X	X	X	X	X						X	X	X	X	X	X	X	
Meals		X	X	X	X	X	X	X						X	X	X	X	X	X	X	
Informed Consent	X																				
Medical History	X	X																			
Comprehensive Physical Exam	X																				X
Targeted Physical exam		X						X						X						X	
Vital signs	X	X						X						X						X	X
Height/Weight	X	X																			X
ECG - single	X	X																			X
Urinalysis	X	X																			X
Urine cotinine test	X	X																			
Urine drug screen + alcohol screen	X	X												X							
Pregnancy test (females only)	X	X																			X
FSH (females only)	X																				
COVID19 Test		X												X							
HIV Test	X																				
Hepatitis Test	X																				
Dosing DDI Substrate Drug			X												X						
CBD Dosing (oral)								X	X	X	X	X	X	X	X	X	X	X	X		
PK Samples			8	1	1	1	1	1							8	1	1	1	1	1	
Serum Chemistry, Hematology, and Liver function tests (ALT, AST, GGT, ALP, PT/INR, Tbili)	X	X												X							X
Con Med/AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eSource Management		X																			


Days
-1
1
6
12
13
17
18
24
Check-in
Check-out
Check-in
Check-out
Follow-up visit
In-house stay 1 (DDI)
In-house stay 2 (DDI)
CBD Dosing (Days 6-17)
Liver Labs
Drug Interaction
DDI drug (baseline)
DDI drug (with CBD)

Appendix B – Schedule of Events – Part 2.2 (Morphine)

	Screening	Check-in				Treatment Period									Check-out	Follow-up
								Check-out				Check-in				
Study Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	19
In House Residency		X	X	X	X	X	X	X				X	X	X	X	
Meals		X	X	X	X	X	X	X				X	X	X	X	
Informed Consent	X															
Medical History	X	X														
Comprehensive Physical Exam	X															X
Targeted Physical exam		X						X				X			X	
Vital signs	X	X						X				X			X	X
Height/Weight	X	X														X
ECG - single	X	X														X
Urinalysis	X	X														X
Urine cotinine test	X	X														
Urine drug screen + alcohol screen	X	X										X				
Pregnancy test (females only)	X	X														X
FSH (females only)	X															
COVID19 Test		X										X				
HIV Test	X															
Hepatitis Test	X															
Dosing DDI Substrate Drug			X			X							X			
CBD Dosing (oral)						X	X	X	X	X	X	X	X	X		
PK Samples			11	1	1	11	1	1					11	1	1	
Serum Chemistry, Hematology, and Liver function tests (ALT, AST, GGT, ALP, PT/INR, Tbili)	X	X										X				X
Con Med/AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eSource Management		X														


Days
-1
1
4
5
6
10
11
12
13
19
Check-in
Check-out
Check-in
Check-out
Follow-up visit
In-house stay 1 (DDI)
In-house stay 2 (DDI)
CBD Dosing (Days 4-12)
Liver Labs
Drug Interaction
DDI drug (baseline)
DDI drug (with CBD)
DDI drug (with CBD)

Appendix C – List of Abbreviations

LIST OF ABBREVIATIONS	
Abbreviation	**Definition**
AE	adverse event
Ag/Ab	antigen/antibody
AUC	area under the concentration time curve
BID	twice daily
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed concentration
COVID-19	coronavirus disease of 2019
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HepC	hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
K_{el}	elimination rate
Kg	kilogram
LH	Luteinizing Hormone
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PD	Pharmacodynamic
PVD	Pharmacovigilance Department
PK	pharmacokinetic
QA	quality assurance
QD	once daily
QTc	heart rate-corrected QT interval
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
$t_{1/2}$TEAE	terminal half-life treatment-emergent adverse event

Appendix D – Drug-Induced Liver Injury Assessment

The threshold criteria for definition of a case DILI as well as the severity grading score are listed below[15].

Definitions for DILI include one of the following thresholds:

i) ≥ 5 × ULN elevation in ALT (ULN for ALT is 33 U/L for males and 25 U/L for females) OR

ii) ≥ 2 × ULN elevation in ALP (with accompanying elevations of GGT in the absence of known bone pathology driving the rise in ALP level) OR

iii) ≥ 3 × ULN elevation in ALT and simultaneous elevation of bilirubin concentration exceeding 2 × ULN

Severity grading of DILI based on the International DILI Expert Working Group's severity index (4-point scale):

1. Mild: ALT ≥ 5 × ULN or ALP ≥ 2 × ULN and TBL < 2 × ULN
2. Moderate: ALT ≥ 5 × ULN or ALP ≥ 2 × ULN and TBL ≥ 2 × ULN, or symptomatic hepatitis
3. Severe: ALT ≥ 5 × ULN or ALP ≥ 2 × ULN and TBL ≥ 2 × ULN, and symptomatic hepatitis and 1 of the following criteria:
    - INR ≥ 1.5
    - Ascites and/or encephalopathy, disease duration < 26 weeks, and absence of underlying cirrhosis
    - Other organ failure due to DILI
4. Fatal/transplantation: Death or liver transplantation due to DILI

Appendix E – Protocol Revision History

PROTOCOL REVISION HISTORY			
Protocol Number	**Version**	**Effective Date**	**Summary of Changes**
SCR-016	1.0	08 December 2023	1. Developed initial protocol
SCR-016	2.0	21 December 2023	1. Typographical changes made throughout the protocol. 2. Principal investigator updated to Dr. Melanie Fein, MD. 3. Part 1 exploratory endpoint added: "Summary of CBD and metabolite pharmacokinetics." 4. Part 2 exploratory endpoint added: "PK parameters for CBD and metabolites." 5. For Key Exclusion Criteria #1, the threshold for International Normalized Ratio (INR) changed from 1.27 to 1.3. 6. For section 3.1: • Part 1 exploratory endpoint removed "Change from baseline in additional laboratory tests after CBD administration compared to placebo." 7. For section 4.1.1 Risk/Benefit: • The following text removed: "For AEs, acetaminophen 1000 mg q8 hours, as needed, will be provided." 8. For section 4.2.2: • exclusion criteria #8 updated to "Subject has a positive test result for alcohol or drugs of misuse (amphetamines, barbiturates, benzodiazepines, cocaine, alcohol, opiates, phencyclidine,

Protocol Number	Version	Effective Date	Summary of Changes
			propoxyphene, and methadone) at Screening or Check-in (Day -1 [both Parts]; Day 10 [morphine DDI]; Day 12 [citalopram DDI]).” 9. For section 4.2.2: • exclusion criteria #9, added “Day –1” 10. For sections 4.5 Criteria for Subject Withdrawal and 4.7.3.2.1 Assessment and Reporting of Potential Cases of Drug-Induced Liver Injury: • The following language added “When subject withdrawal occurs due to potential Drug-Induced Liver Injury (DILI), the study drug will be discontinued, and monitoring will still be continued to document subsequent liver test results and resolution of biochemical abnormalities.” • Follow-up liver assessment timing changed from to “24 to 48 hours.” • Language added: “These follow-up steps are outlined in more detail in Supplement A: LFT Elevation Evaluation.” 11. For section 4.5.1 Handling of Withdrawals, removed, “Any data and samples collected before subject withdrawal will become the property of the sponsor.” 12. For sections 4.6.3 Screening and 4.6.4.1 Check-In (Day -1): • “Cannabinoids (THC)” added to list of drugs screened for. • Added the following testing language: “Perform FSH assessment

Protocol Number	Version	Effective Date	Summary of Changes
			(postmenopausal [i.e., spontaneous amenorrhea for at least 12 months] female subjects only)." 13. For section 4.6.4.1 Check-in (Day –1) and Part 1 SOE, complete physical exam changed to targeted physical exam and a weight collection added to list of assessments. 14. For section 4.7.2 Lipid Assessments, added "Lipid assessments will include total cholesterol, LDL, HDL, and triglycerides." 15. For section 4.8.7 Subject Restrictions and 4.2.2 Exclusion criteria, kava melatonin and St Johns Wart added to list of exclusion criteria and restricted supplements. 16. For section 4.9.2 Analysis Populations, added the following language: • "...with the substrate drug alone and with the substrate drug in combination with CBD." 17. For section 4.9.6 Additional Analyses, added: • "...the following categorical and visual summaries." • "Steady state CBD and metabolite drug concentrations will be summarized by visit using descriptive statistics." 18. Appendix B updated to accurately reflect events.
SCR-016	3.0	19th March 2024	1. For synopsis and section 4.1 Study Design, added the language "…to remind subjects regarding their requirements for…"

Protocol Number	Version	Effective Date	Summary of Changes
			2. For section 4.2.1 Inclusion Criteria, added "Day -1" to inclusion number 2 and 4. 3. For section 4.2.2 Exclusion Criteria, exclusion #1 was updated to include "screening or check-in (Day -1)" and #12 was further updated to add "a diagnosis of COVID-19" 4. For section 4.2.2 Exclusion Criteria, exclusion #16 added "Uncomplicated cholecystectomies and appendectomies may be included at the investigator's discretion." 5. For section 4.2.2 Exclusion Criteria, blood pressure values updated to the following: "Subject has a mean systolic blood pressure <85 or >145 mmHg or a mean diastolic blood pressure <45 or >95 mmHg at either Screening or Check-in. 6. For section 4.6.4.2 Treatment, "Collect whole blood sample for pharmacogenetic testing (Only Part 2)" was added and removed from 4.6.4.1 Check-in 7. For section 4.6.4.2 Treatment, added "Administration of study drug [Part 1: clinic visits and Day 28, Part 2: Day 12 (citalopram) and Day 10 (morphine)] can occur prior to review of safety labs." 8. For section 4.7.1.1 Pharmacokinetic Sample Collection " Clinic visits may be completed outside of the listed visit day per investigator's decision." And " All lab collections will take place predose and within 1 hour of mealtime" was added.

Protocol Number	Version	Effective Date	Summary of Changes
			9. For section 4.7.3.3 Vital Sign Measurements, added “Vital signs may be repeated at investigator discretion.” 10. For section 4.8.6 Prior and Concomitant Medications, removed “oral” from “oral contraceptives” and added “During the study, low dose acetaminophen or ibuprofen may be allowed with investigator’s approval for minor symptoms.” 11. For Appendix A and B Schedule of Events and Section 4.6.4.1, pharmacogenetic testing was removed 12. For Appendix A and B Schedule of Events, “PCR” removed from Covid testing

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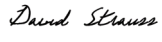
David Strauss david.strauss@fda.hhs.gov Sponsor Study Lead Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: C37632FD-56B7-47FC-9B70-FAEE64302722 Using IP Address: 150.148.14.141 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 3/20/2024 9:34:05 AM Resent: 3/21/2024 9:53:29 AM Viewed: 3/21/2024 9:56:11 AM Signed: 3/21/2024 9:56:34 AM
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