Statistical Analysis Plan

Study Title:	**Cannabidiol Effects on Craving and Relapse Prevention in Opioid Use Disorder**
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Statistical Analysis Plan Approval

Cannabidiol Effects on Craving and Relapse Prevention in Opioid Use Disorder

I confirm that I have reviewed this document and agree with the content:

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Introduction

The following Statistical Analysis Plan (SAP) describes the planned analysis and data presentations for "Cannabidiol Effects on Craving and Relapse Prevention in Opioid Use Disorder", protocol version dated 08 June 2023. Changes to the protocol may result in subsequent changes to the SAP.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the primary and secondary RCT data analyses prior to database lock. This SAP will be finalized and signed prior to the clinical database lock for the final analysis. Any significant changes after the final database lock will be documented in a final SAP Amendment. All statistical analyses detailed in this plan will be conducted using SAS® 9.4 or a later version.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to examine study data further. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

1. Glossary of Abbreviations

AE	Adverse Event
2-AG	2-Arachidonoylglycerol
ALT	Alanine transaminase
AST	Aspartate transaminase
Bup	Buprenorphine
CBD	Cannabidiol
ConMeds	Concomitant medications
COWS	Clinical Opiate Withdrawal Scale
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CYP3A	Cytochrome P450, family 3, subfamily A
DDQ	Desires for Drug Questionnaire
DSMB	Data safety monitoring board
EDDP	2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine
EKG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
HIV	Human immunodeficiency virus
Hg	Mercury
HR	Heart rate
IMP	Investigational medicinal product
InfCons/Demogr	Informed consent/demographics
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MedHx/PsychHx	Medical history and psychiatric evaluation
MFA	Multi-factor authentication
MINI	Mini International Neuropsychiatric Interview 7.0.2 for DSM-5
NorBup	Norbuprenorphine
OAAS	Observed Observer's Assessment of Alertness/Sedation Scale

OUD	Opioid use disorder
PACS	Penn Alcohol-Craving Scale adapted for opioid craving
PANAS	Positive and Negative Affect Schedule
PI	Principal investigator
PK	Pharmacokinetic
PO	Per os (orally)
QRS	Combination of the Q, R and S waves (QRS complex), representing ventricular
QT	Time from the start of the Q wave to the end of the T wave on EKG
QTc	Corrected QT interval
SAP	Statistical analysis plan
SOC	System organ class according to the MedDRA dictionary
SOP	Standard operating procedure
STAI	Spielberger State-Trait Anxiety Inventory
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine-binding globulin
THC	Tetrahydrocannabinol
THS	Thyroid-stimulating hormone
ULN	Upper limit of normal

2. Background

Opioid Use Disorder (OUD) is a public health emergency leading to unprecedented drug-related mortality in the United States,[1-3] underscoring the need for innovative medical treatments. Three medications are FDA-approved for treatment of OUD, but retention in treatment is low even with medication.[4,5] Positive findings from preclinical and clinical studies provide a rationale for the use of cannabidiol (CBD) in treatment of OUD. Notably, a Phase 2, randomized, double-blind, placebo-controlled, pilot study found that a single dose of CBD (400 or 800 mg) decreased cue-induced opioid craving and blunted anxiety.[6,7] Still, rigorous clinical trials are needed to establish the value of CBD as adjunctive therapy for OUD.

Based on prior work, CBD is expected to be well-tolerated and safe in patients with OUD,[6,7] but safety signals (vital signs and laboratory test results) will be assessed in more detail here. Specifically, because CBD inhibits cytochrome P450 isozymes including CYP3A,[8] the primary mechanism for hepatic buprenorphine N-dealkylation, we will evaluate whether CBD poses potential safety concerns associated with buprenorphine treatment. Specifically, we will seek to evaluate the frequency and magnitude of this possible drug-drug interaction to ensure safe and effective treatment of OUD for patients receiving medication-assisted treatment with buprenorphine. In addition to assessing safety, this study will provide preliminary information on the efficacy of CBD compared with matched placebo as an adjunctive treatment in patients receiving medication-assisted treatment for OUD.

Beyond the safety and efficacy objectives, prior research indicated that CBD increases fatty acid amide hydrolase, the principal enzyme catalyzing catabolism of the major endocannabinoids anandamide and 2-AG.[9-11] More recent work, however, indicates that CBD inhibits anandamide uptake into cells.[12] As such, CBD administration may affect plasma concentrations of these endocannabinoids. Plasma levels of anandamide and 2-AG will be assayed to explore whether CBD increases their concentrations in this study.

3. Study Overview

3.1. Study Design, Blinding, and Randomization

This is a randomized, double-blind, placebo-controlled, phase 2 trial to evaluate the safety and efficacy of CBD as adjunctive therapy in patients receiving medication-assisted inpatient treatment for OUD. It is a single-site study, conducted at a residential treatment center. The original plan was for ~60 subjects to be randomized (2:1 CBD:placebo) for study in two ascending dose cohorts, the first receiving CBD 600 mg/day orally (PO) (n =20) or placebo (n = 10) and the second receiving CBD 1200 mg/day PO (n = 20) or placebo (n = 10), ultimately creating three equal arms. Due to budgetary constraints, the higher-dose cohort was eliminated, and the randomization ratio was reversed to 2:1 placebo: CBD 600 mg/day towards the end of the lower-dose segment of the study to balance the remaining two arms as much as possible. This SAP is based on data from 28 participants randomized using a 2:1 CBD 600 mg/placebo ratio and 7 participants randomized using a 2:1 placebo:CBD 600 mg ratio.

Study Periods: The study design comprised four phases: 1) a 14-day screening period during which patients were consented, evaluated against entry criteria, and stabilized on buprenorphine; 2) randomization and baseline evaluation (Day 0); 3) a 28-day acute treatment period when each participant received the IMP twice daily (CBD or placebo); primary data collection phase, and 4) a 28-day follow-up period after termination of treatment with study medication (secondary data collection phase). Safety assessments included clinical lab tests during screening and weekly during the treatment and follow-up periods. On each study day, vital signs were taken, and patients reported adverse events, which were monitored and recorded. Although not a direct measure of safety, change in buprenorphine metabolism, operationalized as the ratio of buprenorphine to norbuprenorphine in plasma, was obtained, as out of range values occuring in the context of hypoxia and/or sedation could be indicative of increased risk. Because CBD inhibits CYP3A,[8] the primary mechanism for hepatic buprenorphine N-dealkylation, the buprenorphine to norbuprenorphine ratio was measured in blood drawn for relevant PK analyses at baseline and weekly during the treatment and follow-up periods. Cue-induced craving was measured in laboratory sessions with a paradigm in which neutral and opioid-related cues were presented. These sessions were conducted before dosing on Day 0 (Baseline) and on Days 7 and 28 after study drug initiation (Treatment Phase).

The original protocol was approved by the FDA on October 12, 2020 (IND 152888). Modifications were needed because the approved investigational product became unavailable. On October 27, 2021, the FDA approved using ATL5 (100 mg/ml CBD softgel capsules) and matching placebo as the investigational medicinal products (IMPs), and testing two ascending-dose cohorts [cohort 1: CBD 600 mg/day, N = 20 and placebo (N = 10); cohort 2: CBD 1200 mg/day, N = 20 and placebo, N = 10)], each randomized 2:1 CBD:placebo, with the combined placebo subsamples intended to be treated as a common reference for both drug groups. The trial commenced in March 2022.

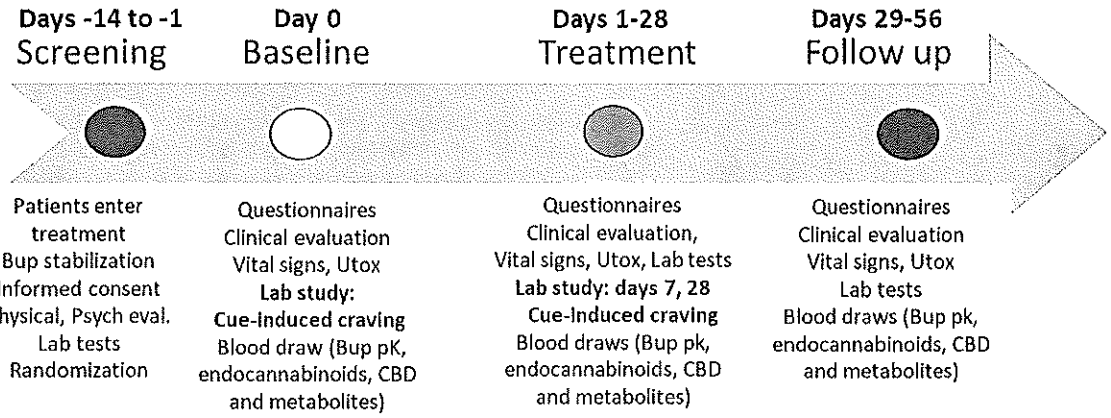
Randomization was stratified by baseline (i.e. post-stabilization period) plasma buprenorphine level—either < 2 ng/mL or ≥ 2 ng/mL—measured immediately prior to randomization and the daily dose of buprenorphine.

From May 2022 through May 2003, 28 participants were randomized 2:1 CBD 600 mg:placebo; however, 6 of these participants did not receive any study drug.

Towards the end of enrollment of the first dose cohort, it became clear that financial constraints would preclude study of a higher dose cohort. In June 2023, randomization was reversed to 2:1 placebo:CBD to increase power by balancing the low CBD and placebo groups as much as was

possible in the remaining time. From June 2023 through January 2024, 7 participants were randomized 2:1 placebo:CBD 600 mg. This SAP is based on the study plan that includes these modifications. It is expected that there will be 21 patients in the 600-mg CBD arm (28*0.67+7*.33), and 14 patients in the placebo arm (28*0.33+7*0.67).

3.2. Figure of Study Design



3.3. Schedule of Events

	Stabilize on BUP	BUP PK	Determine Eligibility	TREATMENT										Follow-up	
Study day →	-14 to -7	-7	-7 to 0	0	1,2,4-6	3	7	8-13	14	15-20	21	22-27	28	29-31, 33	35,42,49,56
IC/IEC/Demogs			X												
MINI			X												
C-SSRS			X				X		X		X		X		X
Randomization			X	X											
MedHx/PsychEval			X												
EKG			X										X		
Weight/Height				X									X		
Vitals (HR/BP)				X	X	X	X	X	X	X	X	X	X	X	X
AEs & ConMeds					X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test			X	X	X	X	X	X	X	X	X	X	X		
Urine Drug Screen			X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry				X	X	X	X	X	X	X	X	X	X		
Lab Tests			X				X		X		X		X		X
Ovarian Function			X								X		X		
BUP Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBD Dosing					X	X	X	X	X	X	X	X	X		
PK Sample(s)		X		X		X	X		X		X		X		X
Cue-induced cravings (DDQ)				X			X						X		
COWS				X	X	X	X	X	X	X	X	X	X	X	
PACS, STAI, PANAS, OAAS			X	OAAS/ only	X	X	X	X	X	X	X	X	X	X	X

3.4. Objectives and Endpoints

Objectives	Endpoints
Primary: To evaluate the safety and tolerability of CBD in the study population.	Primary: Number of treatment-emergent adverse events over the 28-day treatment period by study arm. Secondary: Changes in liver enzymes, pulse oximetry, sedation, and cardiovascular measures (heart rate, blood pressure, and cardiac rhythm and conduction on EKG).
Secondary: To determine the extent to which CBD (600 mg/day) reduces cue-induced craving for opioids relative to placebo.	Primary: Cue-induced craving for opioids, assessed using the Desires for Drug Questionnaire (DDQ)[13] in the context of an opioid cue-induction paradigm, assessed in the laboratory session before CBD dosing on Day 0 (baseline without CBD) and on Days 7 and 28 (after adjunctive treatment with CBD) Secondary: Spontaneous opioid craving, assessed using the Penn Alcohol-Craving Scale, as modified to assess opioid craving;[14] affect, assessed using the Positive and Negative Affect Schedule (PANAS),[15] Anxiety, assessed by state subscale of the Spielberger State-Trait Anxiety Inventory,[16] Percentage of patients with increase in their buprenorphine dose, Treatment retention, as indicated by number of days of continued participation
Exploratory: A. To evaluate effects of CBD on metabolism of other endocannabinoids, i.e., N-arachidonoylethanolamide (anandamide) and 2-arachidonoyl-glycerol (2-AG) levels. B. To assess pharmacokinetics of CBD in patients receiving buprenorphine for treatment of OUD.	Plasma levels of anandamide and 2-AG. CBD pharmacokinetics—time to reach steady state and accumulation parameters (Cmax, AUC_{0-24}). In addition, the buprenorphine/norbuprenorphine ratio will be determined to evaluate potential drug-drug interactions of CBD with buprenorphine metabolism (dealkylation). Although this ratio does not, by itself, an increase in the ratio, concurrent with the emergence of hypoxia and/or sedation would be an AE.

3.5. Sample Size

Sample size is based on the change in cue-induced craving from baseline to 28-days, the end of the acute treatment period. The actual number of subjects enrolled has changed since the initial protocol. This section will focus on the standardized effect size needed to show 1-sided significance level of $\alpha = 0.025$ (equivalent to $\alpha = 0.05$ two sided but reflecting our directional hypothesis), based on 21 treated and 14 placebo subjects. Based on the SAS power calculation below, if there is a standardized effect size of d = 1.0, then there is a power of 0.80.

```
proc power;
  twosamplemeans test=diff
    groupmeans = 0 | 1
    stddev = 1
```

```
    groupweights = (14 21)
    ntotal = 35
    power =. ;
run;
```

4. Statistical Considerations

4.1. General Considerations

All key data collected on case report forms will be presented in the data listings and will be listed and sorted by treatment arm, participant number and (where applicable) visit. All descriptive summaries will be presented by treatment group and (where applicable) nominal visit/time point.

All safety and descriptive summaries will be presented by treatment group. All disposition and concomitant medication descriptive summaries will be presented by treatment sequence and nominal visit/time point (where applicable).

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean, SD and median values will be displayed to one more decimal than the source data for the specific variable.

  95% Confidence Intervals (CIs), mean differences (among treatments and from baseline) and least-square (LS-Means) values will be displayed to one more decimal than the source data for a specific variable. P-values will be displayed to 3 decimal places.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the afore-mentioned rules.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place. Proportions will be displayed to 3 decimal places.

  95% Confidence Intervals (CIs), difference in proportions, odds ratios and other categorical parameters will be displayed to one decimal place for percentages. Proportions will be displayed to 3 decimal places. P-values will be displayed to 3 decimal places.

  No inferential statistics will be produced for any safety endpoints.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. Unscheduled visit data may be included in summaries of baseline, minimum/maximum post-baseline, and incidence of subjects with potentially

clinically significant post-baseline results. Unscheduled visits will also be presented in the applicable data listings.

- Assessment windows: Data will be summarized using the recorded nominal visit values in the CRF; no visit date windowing will be conducted. All assessments will be included in the data listings.

- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:

  Date only: YYYY-MM-DD
  Date and time: YYYY-MM-DD HH:MM

  If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Times will be reported in military time.

4.2. Handling of Missing Data

For the classification of Treatment emergent adverse event (TEAE) and concomitant medication, the following will be applied in the described order:

a. If all dates/times (start and stop) are missing, the event/medication will automatically be classified as a TEAE/concomitant medication.
b. For AEs with a missing start date/time, if the event end date/time is prior to first instillation, the event will not be classified as a TEAE.
c. If only the AE start year/ medication end year is present and is the same or is after the first instillation year unit, the event/medication will be classified as a TEAE/concomitant medication.
d. If the AE start month and year/medication end month and year are present and are the same or after the first instillation month and year units, the event/medication will be classified as a TEAE/concomitant medication.

4.3. Conversion of categorical values

In some instances, continuous variables are expressed as a range (i.e., < 10). In such cases, values may be converted to the range boundary (upper or lower limit as applicable). As an example, a value of <10 may be converted to 10. Such substitutions will be clearly documented in the footnotes of relevant outputs.

4.4. Coding of Events and Medications

Medical history and AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analyses.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Medications will be mapped to the full WhoDrug Anatomical Therapeutic Chemical (ATC) class hierarchy, but PTs will be of primary interest in this analysis.

5. Analysis Populations (Analysis Sets)

The randomized population will include all subjects randomized regardless of whether they had any study drug.

The safety population will include all subjects who received at least one treatment of study drug and will be used for the summaries of all baseline, demographic, and safety data.

The full analysis set (FAS) population is a subset of safety population and consists of those that have at least one post-baseline efficacy measurement. This population will be used for the summaries of all efficacy data.

The pharmacokinetic (PK) population is a subset of the safety population and consists of those who have at least one PK assessment.

6. Disposition

Participant disposition will be based on the randomized population and include the number in each of the other study populations, as well as the number of subjects that completed each of the study visits, and, for those who did not, the reason for early withdrawal. A listing corresponding to the disposition table and a listing for screen failures will be provided.

7. Protocol Deviations

Prior to database lock, all protocol deviations will be reviewed by medical monitor and assigned a status of minor or major. A listing of all major protocol deviations will be provided.

8. Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized and listed. Medical history, the psychological evaluation, and the MINI will also be summarized and listed. In both cases, this will be based on the randomized population.

9. Study Drug Exposure

Study drug exposure will be summarized and provided in a listing, based on the randomized population.

10. Safety

Safety endpoints will be analyzed using the Safety population.

10.1. Adverse Events

AEs related to study procedures will be collected from the signing of the ICF through the end of the study. An adverse event (AE) will be recorded if it is a new event that was not present at Screening or is the worsening of an event present at Screening.

All AEs included will be coded using MedDRA. All AE summaries will be restricted to TEAEs only. Summary tables will include the number of participants (%) experiencing an event and the number of events. Participants will be counted only once for each SOC and PT level (categorical descriptive analysis). When TEAEs are reported by relatedness and/or severity, each TEAE will be counted once per subject at the worst/highest level of the assessment (e.g., highest relationship to investigational device or greatest severity).

The MedDRA version used for reporting will be described in the relevant table and listing footnotes.

The TEAE summaries will include:
- Overall summaries of TEAEs.
- TEAE summaries by SOC and PT.

A comprehensive listing of all adverse events will be provided in a by-subject data listing.

10.2. Safety Laboratory Assessments

Only key lab parameters as outlined in Appendix A will be provided in a table. These results will be summarized and provided in a listing.

Pregnancy test data (urine and serum based) findings will be presented in by-subject data listings for any non-negative result.

10.3. Vital Signs

The following vital signs measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol): Height (cm), Weight (kg), Heart Rate (beats/min), Systolic blood pressure (SBP) (mmHg), Diastolic blood pressure (DBP) (mmHg), Respiratory rate (breaths/min), Temperature (°C). All vital signs data will be summarized and included in the listings.

10.4. Concomitant Medications

Concomitant medications will be summarized by indication and drug name, as well as provided in a listing.

11. Efficacy

All efficacy analyses will be based on the Full Analysis Set Population and Efficacy endpoints will be summarized descriptively. Absolute change and percent change will be reported for all efficacy endpoints. All efficacy data will be provided in listings.

Primary Efficacy Target

Desire for Drug Questionnaire (DDQ): The DDQ is a 14-item scale used to assess cue-induced craving, administered here in the context of a laboratory-based opioid cue-induction paradigm. All responses are scored on a Likert scale from "strongly disagree" (1) to "strongly agree" (7). A table will be provided with summaries per visit (Baseline, 7, and 28 days), as well as absolute and percent changes from baseline, for the DDQ Total Score of Opiate Use (subscale including 7 items, primary endpoint) and the DDQ Total Score (all 14 DDQ items, secondary endpoint), both of which will be used to assess cue-induced craving, our primary efficacy target. For each outcome, we will run a mixed model for repeated measures (MMRM), with change from baseline as the outcome; fixed effects for treatment, time, and a treatment by time interaction; and an appropriate random effects/covariance structure to account for within-subject correlations. In addition, figures, based on the MMRMs will be provided: 1) by treatment, and 2) for the difference between treatments, both with 95% model estimate confidence intervals. The primary efficacy outcome is the MMRM model estimate for change from baseline in cue induced craving at 28 days between the two treatment groups.

Secondary Effiacy Outcomes

Clinical Opiate Withdrawal Scale (COWS): The COWS is an 11-item measure of opiate withdrawal with Likert-type responses ranging from 0 to 5 or 0 to 4, depending on the particular item. There is no reverse scoring. The total COWS score is taken as the sum of all items. A table and plots similar to those for DDQ will be created encompassing all the available visits (Baseline to Day 33) for the COWS total measurement.

Penn Alcohol Craving Scale (PACS; adapted for opioid craving): The PACS is a 4-item scale to assess spontaneous craving with Likert-type responses ranging from 0 to 6. PACS summary scores will be calculated by summing the responses on all 4 items since no reverse scoring is required. Tables and plots will be provided as above.

State Trait Anxiety Inventory (STAI); State Scale: The STAI State scale is a 20-item measure of state anxiety with Likert-type responses ranging from "not at all" (1) to "very much so" (4). For half of the items (items 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20), reverse scoring is required in which case the responses range from "not at all" (4) to "very much so" (1). After reverse scoring, all 20 items are summed to provide a total score. Tables and plots will be provided as above.

Positive and Negative Affect Schedule (PANAS)-Positive Affect Scale: There are 30 items on the PANAS with Likert-type responses ranging from "Very Slightly or Not at All" (1) to "Extremely" (5). There is no reverse scoring. For the PANAS Positive Affect Scale, 15 items are summed: #'s 1, 2, 5, 6, 7, 13, 14, 15, 17, 19, 21, 24, 25, 26, and 28. Tables and plots will be provided as above.

Positive and Negative Affect Schedule (PANAS)-Negative Affect Scale: There are 30 items on the PANAS with Likert-type responses ranging from "Very Slightly or Not at All" (1) to "Extremely" (5). There is no reverse scoring. For the PANAS Negative Affect Scale, 15 items are summed: #'s 3, 4, 8, 9, 10, 11, 12, 16, 18, 20, 22, 23, 27, 29, and 30. Tables and plots will be provided as above.

12. Pharmacokinetic Analyses and Effect on Endogenous Cannabanoids

All pharmacokinetic analyses will be performed using nominal times due to the limited amount of actual time data available.

Noncompartmental analysis (NCA): On Day 0, 14, and 28, the following NCA parameters will be calculated for CBD and its metabolites: Cmax, Tmax, and AUC0-24. Half-life will be estimated on Day 28, as data permit. Time to steady-state will be evaluated graphically based on trough concentrations. Accumulation ratios for Cmax and AUC0-24 will be estimated on Days 14 and 28 relative to Day 0.

Buprenorphine (bup) and norbuprenorphine (norBup) NCA parameters of Cmax, Tmax, and AUC0-24 will be calculated on Day 0, 14, and 28.

Bup and norBup drug interaction assessment: Bup and norBup Cmax and AUC0-24 accumulation ratios (geometric mean ratios) will be estimated for those who do and do not receive CBD to assess the potential for drug interactions. We will then use an ANCOVA model with body weight as a covariate to compare the groups. Any patient who changed Bup dose during the study will not be included in drug interaction evaluations.

In exploratory analyses, to determine whether treatment with CBD affects plasma concentrations of anandamide and 2-AG, we will run separate MMRM analyses with group (600 mg CBD or placebo), time and their interaction as predictors and changes in anandamide and 2-AG as the dependent variables, respectively.

13. Changes to the Planned Analysis

Not applicable.

14. Timing of the Analysis

No interim analysis is required. The final analysis will be performed after database lock and unblinding.

15. Software

SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) will be used for all non-pharmacokinetic analyses. NCA parameters will be calculated using PKNCA version 0.11 or higher.

16. References

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17. Appendices

APPENDIX A. REFERENCE RANGES FOR CLINICAL LAB TESTS

Category	Test	Reference Range
CBC, Platelets and Differential	White Blood Cell Count	4.16-9.95 x10E3/uL
	Red Blood Cell Count	3.96-5.09 (female); 4.41-5.95 (male)
	Hemoglobin	11.6-15.2 g/dL (female); 13.5-17.1 g/dL (male)
	Hematocrit	34.9-45.2% (female); 38.5-52.0% (male)
	Mean Corpuscular Volume	79.3-98.6 ng/mL
	Mean Corpuscular Hemoglobin	26.4-33.4 pg
	MCH Concentration	31.5-35.5 g/dL
Comprehensive Metabolic Panel	Albumin	3.9-5.0 g/dL
	Alkaline phosphatase	37-113 U/L
	Alanine Aminotransferase (ALT)*	8-70 U/L
	Aspartate Aminotransferase (AST)*	13-62 U/L
	Bilirubin, total*	0.1-1.2 mg/dL
	Calcium	8.6-10.4 mg/dL
	Chloride	96-106 mmol/L
	Total CO2	20-30 mmol/L
	Creatinine	0.60-1.30 mg/dL
	Glucose	65-99 mg/dL
	Potassium	3.6-5.3 mmol/L
	Total Protein	6.1-8.2 g/dL
	Sodium	135-146 mmol/L
	Urea Nitrogen	7-22 mg/dL
Urinalysis	Specific Gravity	1.005-1.030
	pH	5.0-8.0
	Protein, Bilirubin, Glucose; Ketone bodies; Blood; Nitrites; Leukocyte	All Negative
	RBCs per µL	0-11 cells/uL
	WBCs per µL	0-22 cells/uL
	Squamous epithelial cells	0-17 cells/uL
Coagulation	INR*	In absence of anticoagulant therapy: < 1.1 Therapeutic range: 2-3; Mechanical valves: 2.5-3.5
Additional Tests, Hormone	Estradiol	Female: Prepubertal: <12 pg/mL; Postmenopausal: <21 pg/mL; Follicular phase: 20-100 pg/mL; Mid-cycle: 80-400 pg/mL; Luteal phase: 30-220 pg/mL Male: Prepubertal <12 pg/mL; Adult <41 pg/mL
	Prolactin	Female: 3-23.1 ng/mL; Male: 3.8-18.9 ng/mL
	FSH Blood	Female: Prepubertal: 1-6 mIU/mL; Pregnant: <6 mIU/mL; Postmenopausal: 21-106 mIU/mL; Follicular phase: 2-8 mIU/mL; Mid-cycle: 6-23 mIU/mL; Luteal phase: 1-6 mIU/mL Male: Prepubertal: 1-6 mIU/mL; Adult 1.6-9 mIU/mL
	LH	Female: Prepubertal: 1-3 mIU/mL; Postmenopausal: 16-63 mIU/mL; Follicular phase: 2-15 mIU/mL; Mid-cycle: 10-91 mIU/mL; Luteal phase: 1-15 mIU/mL Male: Prepubertal: 1-3 mIU/mL; Adult: 2-12 mIU/mL
	TSH	0.3-4.7 mcIU/mL
	T4, Total	4.90-11.40 mcg/dL
	T3, Total	85-185 ng/dL
	Free T4	4.5-10.5 ng/dL

*Key lab endpoints

APPENDIX B. CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES (PCSAs)

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor (NIDA) according to predefined criteria/thresholds based on literature review and defined by the Sponsor. Given the literature and safety findings with Epidiolex®, a currently FDA-approved and marketed drug, and considering the possibility of untoward drug-drug interactions of CBD with buprenorphine, PCSA criteria are related to potential drug-induced liver injury, blood clotting, hypoxia related to an effect of CBD on buprenorphine metabolism, and ovarian suppression.

Potential Cases of Drug-Induced Liver Injury

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be considered as meeting criteria for a PCSA:

1. Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥ 3 times the upper limit of normal (X ULN) concurrent with total bilirubin ≥ 2 X ULN with no evidence of hemolysis and alkaline phosphatase ≤ 2 X ULN or not available.

2. For subjects with preexisting ALT **OR**, AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

   AST or ALT ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X ULN (whichever is smaller).

3. For subjects with pre-existing values of total bilirubin above the normal range: total bilirubin increased by one time the upper limit of normal or ≥ 3 times the upper limit of normal (whichever is smaller).

Potential Cases of Drug-Drug Interaction to induced Increase in Blood Clotting

Increase in buprenorphine levels with excessive sedation and slow respiratory rate, with hypoxia (<90%) on room air. Sedation is assessed with the Observed Observer's Assessment of Alertness/Sedation Scale (OAAS) with pulse oximetry data. A score of <4 on the OAAS scale or pulse oxygen saturation less than 92% in room air.

Potential Cases of Ovarian Suppression

For women, values outside the reference ranges on a hormonal battery [estradiol, follicle-stimulating hormone, free thyroxine index, luteinizing hormone, prolactin, T3 uptake, thyroid-stimulating hormone, and thyroxine], followed by an abnormal ovarian ultrasound finding.