Statistical Analysis Plan

A Phase 2, Open-label, Dose-finding Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Pediatric Patients with Treatment-Resistant Childhood Absence Seizures

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Statistical Analysis Plan

Sponsor:	Insys Development Company, Inc.
Protocol No:	INS011-17-103
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Title:	A Phase 2, Open-label, Dose-finding Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Pediatric Patients with Treatment-Resistant Childhood Absence Seizures
CRF Version No./Date:	0.1/27-Nov-2017
SAP No.	1.0

Approvals

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1.0 Introduction

This Phase 2 study is designed to determine the effect CBD has on Childhood Absence Seizures, to inform future studies.

The statistical analysis plan (SAP) is based on:

- Protocol No. INS011-17-103, dated 27-Sep-2017
- CRF dated 27-Nov-2017
- ICH guidelines E4 (Dose-Response Information to Support Drug Registration) and E9 (Statistical Principles for Clinical Trials)[1,2]
- Discussions with the FDA

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and efficacy data for Study Protocol No. INS011-17-103.

The SAP is to be developed in two stages. The purpose is to "finalize" the SAP so that we can start programming earlier in the process. Versions of the SAP up to initial sponsor approval will be known as the SAP. Changes following approval of the SAP will be tracked in the SAP Change Log and a final version of the SAP, known as the Amended SAP, will be issued for sponsor approval prior to database lock.

2.0 Study Objectives

Primary Objective

- To assess the efficacy of Cannabidiol Oral Solution in the treatment of pediatric patients with treatment-resistant childhood absence seizures.

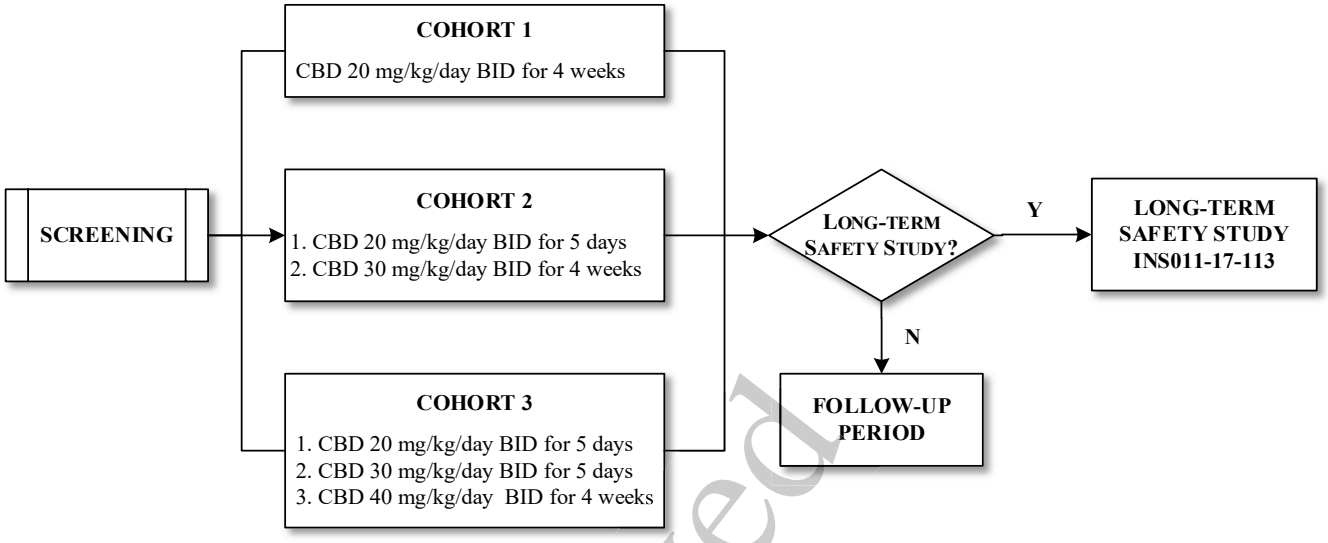
Secondary Objectives

- To assess any improvement in qualitative assessments of patient status over the duration of the study.
- To assess the safety and tolerability of Cannabidiol Oral Solution treatment in pediatric patients with treatment-resistant childhood absence seizures.
- To assess the pharmacokinetics of Cannabidiol Oral Solution in pediatric patients with treatment-resistant childhood absence seizures.

3.0 Study Design

This is a Phase 2, open-label, dose-finding study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of three doses (20, 30, and 40 mg/kg/day) of Cannabidiol Oral Solution in a sequential fashion. Doses exceeding 40 mg/kg/day will not be examined in this study. The study design and patient progression throughout the study is outlined in Figure 1.

Figure 1: Study Design Schematic



NOTE: All patients in Cohort 1 will be treated for 4 weeks prior to initiation of enrollment into Cohort 2, and all patients in Cohort 2 will be treated for 4 weeks prior to initiation of enrollment into Cohort 3.

FOLLOW-UP PERIOD: Patients who do not choose to enroll in the long-term safety study will taper their dose and receive a follow-up 4 weeks after taper completed.

Eligible patients will have a Baseline video-EEG that will include hyperventilation. Video-EEG will be repeated at the end of the treatment period to assess efficacy.

The study drug will be added to existing antiepileptic drug (AED) therapy for the Treatment Period. Dosages of concomitant AEDs will be held constant for the Screening Period and during the 4-week Treatment Period.

The study will consist of 30 patients spread equally across the 3 dose cohorts and will be conducted in the United States of America across 8 study centers. Patient treatment group is not blinded in this study.

Patients will be male and non-pregnant female volunteers between ages 3 and 17 years (inclusive) at time of consent who were diagnosed with childhood absence epilepsy (CAE) between ages 3 and 12 (inclusive), have an average of ≥ 5 absence seizures per day, weigh ≥ 10 kg, patient and/or parent(s)/caregiver(s) are able to understand and provide written consent, have adequate renal and hepatic function, and who meet all the inclusion and exhibit none of the exclusion criteria.

A Data Monitoring Committee (DMC) will meet after all patients in each dose cohort have been treated for at least 4 weeks and provide recommendations regarding escalation to the next dose cohort. This will ensure that the subsequent higher doses are likely to be tolerated. The DMC may also meet on an ad hoc basis if needed. Reference the DMC charter for this study for further detail.

3.1 Sample Size Considerations

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. Cannabidiol has been extensively studied for many indications, including other forms of childhood epilepsy, with favorable tolerability up to 25 mg/kg (Iffland and Grotenhermen, 2017)[3]. The sample size of 30 in an escalating dose design, based on experience from these similar studies to obtain adequate preliminary efficacy, safety, and tolerability data, is thus considered sufficient to achieve the objectives of the study.

3.2 Randomization

This is a non-randomized study. Patients will be enrolled sequentially in escalating dose groups.

4.0 Study Variables and Covariates

4.1 Primary Efficacy Variable

The primary outcome variable is the percent change in absence seizure count using video-EEG collected at Baseline and Week 4 (Visit 5), comparing doses.

4.2 Secondary Variables

Efficacy assessments will also include:

- percent change in time to first absence seizure after initiation of hyperventilation testing on video-EEG from Baseline to Week 4 (Visit 5)
- percent of patients seizure free at Week 4 (Visit 5)
- investigator CGI-I score at Week 4 (Visit 5)

4.3 Safety

Safety assessments will include medical history and conditions, prior and concomitant medications (AEDs and others), vital signs, C-SSRS[4] and AE assessments, and physical and neurological examinations. Blood samples will be taken for clinical laboratory tests (chemistry and hematology), urine will be collected for urinalysis, and the 12-lead ECG will be performed according to the Schedule of Events (Figure 1).

All adverse events will be documented at every visit. Adverse events will be classified by severity and relationship to study drug using The Medical Dictionary for Regulatory Activities (MedDRA, version 20.0 or higher) as described in the protocol. The incidence, type, and severity of AEs and serious adverse events (SAEs) occurring during the Treatment Period (i.e., treatment-emergent adverse events [TEAEs]) will be summarized to meet safety endpoints. Overall summary of TEAE's will be summarized by any TEAE, treatment-related TEAE, treatment-related and severe TEAE, TEAE leading to study drug discontinuation, any serious TEAE, any serious and treatment related TEAE and TEAE resulting in death. Summaries of AEs will include incidence of TEAEs and treatment-related TEAEs by MedDRA preferred term (PT) and system organ class (SOC). The TEAEs will also be summarized by severity, PT, and SOC. Subjects reporting more than one TEAE are counted once in each category at the maximum severity. AEs with a start date during the study will be summarized. Listings of all AEs, AEs leading to discontinuation of the study, AEs ongoing into the planned long term safety study, SAEs, and deaths, if any, will be provided.

Vital signs will consist of seated blood pressure, pulse rate, temperature, and respiration rate measurements. Changes from Baseline (Visit 2) in vital signs during the Treatment Period will be summarized to meet safety endpoints.

Hematology assessments include: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC), and platelet count. Serum chemistry assessments include: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), lactate dehydrogenase (LDH), uric acid, glucose, and calcium. Urine assessments include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. Changes from Screening (Visit 1) in laboratory values (hematology, chemistry, and urinalysis) during the Treatment Period will be summarized to meet safety endpoints.

4.4 Predetermined Covariates and Prognostic Factors

For the primary efficacy endpoint of change in number of absence seizure counts, ANCOVA may be applied to compare treatment groups. Factors in the modeling include treatment group and Baseline seizure count from video-EEG recording.

For the secondary efficacy endpoint of change in time to first absence seizure after initiation of hyperventilation testing on video-EEG from Baseline, ANCOVA may be applied to compare treatment groups. Factors in the modeling include treatment group and Baseline time to absence seizure from video-EEG recording.

5.0 Definitions

5.1 Baseline

The Baseline value of any measurement will the most recent valid value recorded prior to administration of the first dose of the study drug during Visit 3. Baseline assessments collected during the Screening Visit (Visit 1) include: historic seizure counts, medical/surgical history, clinical laboratory assessments, the 12-lead ECG, urinalysis, physical examination, height, weight, and C-SSRS. Baseline assessments collected during Visit 2 include: 4-hour video-EEG, seizure diary, past/current AEDs, concomitant medications, concomitant AED blood levels, vital signs, neurological examination, and AEs.

5.2 Change from Baseline

For all study analysis variables Change from Baseline this will be calculated as:

Change from Baseline = Post-Baseline value – Baseline value.

Change from Baseline will only be calculated if both Baseline and post Baseline values are available, unless otherwise specified.

Change from Baseline Status (normal or abnormal) for laboratory values will be defined for each measure based on the measures' classifications as defined by the Central Laboratory.

Visit windows are defined below. If visit timing falls outside of the defined window, the visit will be assigned to the scheduled visit that it occurs closest to.

Visit Windows (Days) Relative to the First Dose of Study Medication

Visit	Relative Target Day/Week	Visit Window
Visit 1 (Screening)	Days -28 to -1	± 5
Visit 2 (Titration)	Titration Days 0-5 or 0-10	± 5
Visit 3 (Treatment)	Day 1	0
Visit 4 (Treatment)	Week 2	0
Visit 5 (Treatment)	Week 4, Day 6	± 3
Visit 6 (End of Study)	Week 4, Day 7	± 3
Early Withdrawal		± 5
Follow-up visit	Week 9	± 5

5.3 Missing values

No imputation of missing endpoint values will be performed. Analysis will be done on all patients in the ITT Population. Patients who are missing a second measurement for the primary efficacy measure will not be included in change from Baseline analyses, but all existing data will be used for analysis of other efficacy and safety measures.

5.4 Completers

A patient is considered to have completed the study if they complete all treatments per assigned cohort and final assessments up to and including week 9, with no early withdrawal.

5.5 Primary variable calculation

The primary variable, percent change in absence seizure counts from video-EEG recording will be calculated by:

Percent change = 100 x ((Count at week 4 – Count at Baseline) / Count at Baseline)

A negative value indicates the percentage of reduction in absence seizures and a positive value indicates the percent increase in absence seizures from Baseline at Week 4 (Visit 5).

5.6 Secondary Variable calculation

The secondary efficacy variable, percent change in time to first absence seizure after initiation of hyperventilation testing on video-EEG from Baseline to Week 4 (Visit 5), will be calculated by:

Percent change = 100 x ((time in seconds at Week 4 – time in seconds at Baseline) / time in seconds at Baseline)

The secondary efficacy variable, percent of patients seizure free at Week 4 (Visit 5), will be calculated by:

Number of patients with zero seizures recorded on seizure diary at Week 4/ Total patients in ITT population.

5.7 Treatment Emergent Adverse Events

Treatment Emergent Adverse Events (TEAEs) are defined as AEs that first occurred or worsened after the first administration of the investigational product, that is after study drug is dispensed and at least one dose is taken. Adverse events are considered treatment-related if the relationship to study drug is indicated as related. A missing relationship will be imputed as related to study drug and included in the summary.

5.8 Dates

Partial missing start dates will be imputed as follows:

Missing Start Date Portion	*Prior to Treatment*	*Same as Treatment Start Date*	*After Treatment Start Date*
Day	*Month and Year < Month and Year of first treatment:* Day = 1	*Month and Year = Month and Year of first treatment:* Day = Day of first treatment	*Month and Year > Month and Year of First Treatment:* Day = 1
Day and Month	*Year < Year of first treatment:* Day = 1, Month = July	*Year = Year of first treatment:* Day = Day of first treatment, Month = Month of first treatment	*Year > Year of first treatment:* Day = 1, Month = January
Day, Month, and Year	To be conservative, completely missing start dates will be set to the date of first treatment		

After following these imputation rules, if the start date is imputed as a date after the end date, the start date will be set to the end date to provide a positive duration for the event incidence. These rules will also be applied to missing Adverse Event dates. Partially missing end dates will be imputed as the Study completion/early withdrawal date.

This is intended to conservatively assign AE start dates relative to treatment start date, when AE start date is partially missing. That is, if the AE start date is partially missing and available information makes it possible that it started after the first day of treatment, then it should be included as a TEAE.

Calculations Using Dates will be performed as follows:

Age will be calculated as Age = Integer [(Date of enrollment – Date of Birth)/365.25].

Study day will be calculated as Study Day = (Date – Date of Visit 3) +1.

Duration of medication with study drug will be calculated as:

Duration* = (Date of last dose – Date of first dose [Visit 3]) +1.

*Note: Missed doses will not be accounted for in the calculation of Duration.

5.9 Age Groups

Age will be categorized into 2 groups 3 to 7 and > 7 to 17 for demographic variable reporting.

5.10 Study Drug Consumed

Given the liquid nature of the study drug, the following method will be used to calculate the amount of study drug used, per bottle, given the displacement of volume in the bottle:

Weight indicates weight of the bottle in grams

Amount consumed in mL =
((Weight at dispensing - Weight at return of bottle) – 0.7 [adapter weight]) / 1.025 [density]

The percent of subjects per treated visits will be calculated as subjects enrolled at each visit vs. total for ITT population

Total amount of doses taken will be calculated as the total of amount consumed for each bottle for all ITT patients.

Total number of doses taken will be calculated as total of both am and pm doses taken, and Dose intensity PDI (mL/week) will be calculated as Cumulative dose (mL) / Duration of medication (weeks) for all ITT patients.

5.11 Body Mass Index

BMI will be reported in kg/m^2. Weight may be collected in kilograms (kg) or pounds (lb) and Height may be collected in centimeters (cm) or inches (in).

For metric measurements kg and cm:

$BMI = Weight/[(Height*100)^2]$

For English measurements lb and in:

$BMI = [Weight/(Height)^2] \times 703$

6.0 Analysis Populations

6.1 Intent-to-Treat

The Intent to Treat (ITT) Population will include all subjects who were assigned to a treatment group and have a Baseline video-EEG administered. Patients who withdraw from the study after completion of the Baseline video-EEG will be included.

The ITT Population will be used for all efficacy assessments and potential sensitivity analyses.

6.2 Per Protocol

The Per-Protocol Population (PP) will include all subjects who complete all treatments, visits, and assessments without major protocol violations. Protocol violations are defined by the FDA as either "*deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being*", or as "*a change, divergence, or departure from the study requirements, whether by the subject or investigator, that resulted in a subject's withdrawal from study participation.*"

For this study, a "major protocol violation" will be defined as:[5,6,7]

- Failure to provide valid informed consent
- Violation of eligibility criteria discovered after study enrollment
- Receipt of excluded concomitant treatments
- Deviation of ± > 20% of the assigned study dose, including receipt of the wrong dose from the study center, under-dosing, over-dosing, missed doses, or extra doses.
- Failure to complete one or more assessments required to calculated any of the primary or secondary efficacy endpoints
- Unreported serious adverse events
- Mishandled samples
- More than 30% of study visits missed or outside permissible windows
- Repeated subject non-compliance with study requirements

Due to the small size of this study, analysis of the PP Population will be exploratory.

6.3 Safety

The Safety Population will include all subjects who were treated with at least one dose of the study drug. The Safety Population will be used for all safety assessments.

6.4 PK

The Pharmacokinetics Population will include all subjects who receive at least one dose of study drug and have at least one usable plasma concentration measurement. The Pharmacokinetics Analysis Population will be used for all Pharmacokinetics assessments.

7.0 Data Monitoring Committee

No interim analysis is planned for this study. However, a DMC will meet on a periodic basis to review safety data. Refer to the DMC Charter for this study for the content, conduct, and timing of TFL delivery for these meetings. Data review meetings will occur after all patients in each dose cohort have been treated for at least 4 weeks.

The DMC analysis will include:

For Demographic data, listings for each patient including age, gender, race and ethnicity, historical seizure count, past and current anti-epileptic drugs, concomitant medications, co-morbid conditions, seizure type and discontinued early including reason for discontinuation. Data will be delivered using JReview listings if a DMC meeting occurs prior to TFLs programming completion.

Safety endpoints data including AEs, changes in vital signs from Baseline, changes in lab values from screening will be provided. The incidence, type, and severity and description fields of AEs and SAEs will be presented for both Treatment and Follow-Up Periods sorted by incidence, and also sorted by severity. AEs will be classified as expected vs. unexpected, and unexpected AEs will be listed first for ease of identification per DMC request. The most common expected AEs are somnolence and diarrhea.

Vital signs will be listed by subject showing Baseline, value at each visit where measured, and corresponding change.

Laboratory values will be listed by subject showing screening, value at each visit where measured and corresponding change.

Data for the safety endpoints will be presented by treatment group side by side, based on stage of the study to evaluate progression to next highest dosing cohort.

Other safety assessments including 12-lead ECG, C-SSRS, medical history, prior medication history, neurological and physical exams, will be listed. ECG data will be listed and presented by treatment group side by side, based on stage of the study to evaluate progression to next highest dosing cohort. If ECG abnormalities occur or QT interval is prolongated as dose escalates, this constitutes a potential stop signal for the study and the DMC may convene for an ad-hoc meeting. C-SSRS description fields will be listed for the DMC upon request.

The following information will be presented by subject (listings only) and overall at the Final Closed Session, unless a signal is observed, which may be reported prior to the final session:

C_{max} maximum concentration

C_{trough} plasma concentration

T_{max} time to maximum concentration

AUC_{0-t} Area under the curve

8.0 Statistical Methods

Tables and data listings will be prepared using SAS Version 9.3 or higher.

General considerations

The results of this study will be reported using summary tables, listings, and figures (TFLs), as appropriate. Continuous variables will be summarized using descriptive statistics: sample size (n), mean, standard deviation (SD), coefficient of variation (CV %) (where appropriate), median, interquartile range, minimum and maximum. Categorical variables will be summarized by presenting the sample size (n), number of events (frequency), and percentage in each category.

8.1 Subject Disposition

Patients who fail screening are not eligible for the study and will not be entered into the database.

The numbers of subjects enrolled, in the ITT Population, in the Safety Population, in the Per-Protocol Population, completing, ongoing to long term safety follow-up and subjects discontinued from the study along with reasons to discontinue from the study, will be tabulated overall and by treatment group. A tabulation of the number and percentage of subjects enrolled at each center will be presented.

Summary tables for withdrawal reasons overall, by study site, and by treatment group will be presented. Withdrawal reasons are as follows:

- Adverse Event
- Death
- Lack of Efficacy
- Lost to Follow-up
- Non-Compliance with Study Drug

- Physician Decision
- Pregnancy
- Protocol Violation
- Site Terminated by Sponsor
- Study Terminated by Sponsor
- Technical Problems
- Withdrawal by Parent/Guardian
- Withdrawal by Subject
- Other

8.2 Important Protocol Deviations

A summary table of protocol deviations will also be presented. All protocol deviations along with patient's eligibility criteria will be listed for the Safety Analysis Population.

Per PRA processes, important protocol deviations data will be entered into our Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS and the resulting set of evaluable subjects throughout the study, adjusting the deviation criteria as seems appropriate. The evaluable subjects set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock. Non-evaluable subjects will not be included in efficacy analyses.

The following important (clinically) protocol deviations, as identified in the clinical trial management system (CTMS), will be summarized by category:

Major

- Eligibility and Entry Criteria
- Incorrect Dose
- Informed Consent
- Missed Efficacy Assessments
- Significant alteration of study drug administration
- Study Drug Compliance

Minor

- Missed Laboratory Assessment
- Missed Scheduled Visit
- Missed Study Procedures
- Other
- Prohibited Concomitant Medication

8.3 Study Drug Exposure and Compliance

Thirty patients in total will be enrolled into one of three dose cohorts (20, 30, and 40 mg/kg/day); ten patients per cohort. Doses will be divided BID and taken within 30 minutes after a meal to ensure consistent plasma levels.

During the Treatment Period, patients will be dosed for 4 weeks during which the investigator will assess tolerability and effect.

Study drug exposure will be calculated in days using the difference between last dose date and first dose date plus one. Missed doses will not be subtracted from the total duration time. The percent of subjects per treated visits, total amount of study drug taken, dose intensity, and PDI will be reported.

8.3.1 Dose Changes

Dose changes are not permitted during this study; however, patients will receive different total doses based on their treatment group and weight. Interruptions, compliance, and dose changes are not included in the calculation of duration of exposure. Study drug exposure data will be presented in a listing of:

- date of first dose
- date of last dose
- total duration of therapy: (date of last dose – date of first dose) +1
- whether each patient completed the full treatment duration
- actual amount of dose in mL
- total medication taken.

Reported compliance issues will be listed and summarized to include:

- unauthorized individual dose modification
- unauthorized multiple dose change
- dose interruption
- dose permanently discontinued
- reason (adverse event, lack of efficacy, PK-analysis result, other)

A patient who experiences several dose modifications for the same reason will be counted only once for this reason. A patient who experiences several dose modifications due to different reasons will be counted once for each reason.

8.3.2 Compliance

Compliance will be assessed using a target of 90% of IP taken with a lower bound of 80% indicating compliance for the ITT population. Patient compliance will be presented in a listing and summarized overall and by treatment group.

8.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD), version March 2017 and will be summarized at each Visit by treatment group, by the number and

percentage of subjects taking each medication, and separately by preferred term for the Safety Analysis Population.

In the event the concomitant medication coincided with an AE, these instances will be listed along with the corresponding AE.

Concomitant Antiepileptic Drugs will be summarized and listed by treatment group.

8.5 Demographic and Baseline Characteristics

Baseline assessments from Visit 1 (screening) will include demographics, past/current AEDs, medical and surgical history, concomitant medications (other than AEDs) vital signs, clinical labs, ECG results, urinalysis, physical and neurological examinations, C-SSRS results and AEs during screening. Baseline assessments from Visit 2 (efficacy Baseline) will include 4-hour video-EEG, seizure diary, meal diary, time to first absence seizure after initiation of hyperventilation. Data listings and summaries (overall and by treatment group) will be provided for both the ITT and Safety Populations.

8.6 Efficacy Analyses

8.6.1 Primary Efficacy Analysis

- Percent change in absence seizure counts comparing treatment at Week 4 (Visit 5) video-EEG to Baseline (Visit 2) video-EEG and comparing doses.

An absence seizure is defined by video-EEG as 3-5 bursts of Generalized Spike Wave (GSW) of 2.7 to 5 hertz lasting ≥ 3 seconds. The number of seizures will be counted from the first seizure beginning after initiation of hyperventilation through the end of the EEG.

The change in number of absence seizure counts will be compared between treatment groups using ANCOVA with Baseline value and treatment groups as factors.

The total measurement time from the video-EEG will be recorded and reported in listings for each subject for both the Baseline and Week 4 (Visit 5) visits. Measurement time is defined as time from initiation of hyperventilation to end of the EEG. If measurement time differs substantially among doses based on their variances, an adjustment term may be included in the percent change in absence seizure counts to make them comparable between patients and between Baseline and Week 4.

All efficacy endpoints will be analyzed using the ITT population.

Primary Efficacy Variable

A positive result for this study will be a reduction in absence seizure counts in any of the dose cohorts.

The percent change in absence seizure counts comparing treatment at Week 4 (Visit 5) video-EEG to Baseline (Visit 2) video-EEG and doses will be analyzed using an ANCOVA procedure.

- Null Hypothesis: There is no difference in the percent change in absence seizure counts between treatment groups.
- Alternative Hypothesis: The percent change in absence seizure counts differs in at least one treatment group.

The Baseline number of absence seizures count, Visit 5 number of absence seizures, and change from Baseline (difference and percent change) will be listed and summarized by treatment group within dosing cohort using descriptive statistics (n, mean, SD, CV%, 90% CIs, median, minimum, and maximum).

Results of the ANCOVA test will be presented in a table along with parameter estimates and the p-value for differences among treatment groups.

Sensitivity analyses for the ANCOVA procedure may be employed if outliers occur, by removing the outliers if total number is small and minimal numbers occur per treatment, to determine the effect on the modeling procedure. Sensitivity analyses may also be employed for missing endpoint data as specified in Section 8.6.4.

Simulation studies have been conducted to show robustness of the ANCOVA procedure at sample size of 10 per group[8]. If results of the ANCOVA analysis procedure yield a significant difference among treatment groups, corresponding power calculations for the detected difference will be presented.

The applicability of the ANCOVA procedure will be assessed through checking of the model assumptions:

- Normally distributed response
- Homogeneity of variance
- Independence and linear relationship between the dependent variables and the covariates
- Homogeneity of regression slopes

These assumptions may be assessed using boxplots to compare treatment group responses and Baseline covariates distribution, quantile-quantile plots for normality of percent change from Baseline as response variable, normal probability plots for homogeneity of residuals, studentized residual plots for residuals across range of percent change responses per treatment group, and scatter plots with regression lines for each treatment group.

The additional assumption of random independent samples will be examined by summarizing and comparing Baseline demographic variables (age, sex, and concomitant AED).

If model assumptions are violated a non-parametric test, the Wilcoxon Mann-Whitney, may be used to perform pairwise comparisons of treatment groups as the primary efficacy analysis with known non-normally distributed data.

The applicability of ANCOVA procedure and comparability of Baseline characteristics will be performed during the study Dry Run meetings to finalize analysis for the SAP sign off and prior to database lock.

8.6.2 Secondary Efficacy Analysis

Secondary Efficacy Variables

Number of daily seizures will be recorded using a seizure diary that captures the number of seizures every day from Screening through the End of Study.

The CGI-I[9] is a 7-point scale that scores the investigator's impression of improvement from 'very much improved' to 'very much worse'. The CGI-I investigator score will be recorded at Week 4 (Visit 5). If a patient withdraws early and does not complete an Early Withdrawal Visit, the investigator will attempt to obtain the CGI-I assessment parents' score at time of withdrawal.

- The percent change in time to first absence seizure after initiation of hyperventilation testing on video-EEG comparing treatment at Week 4 (Visit 5) to Baseline (Visit 2) will be analyzed to compare doses using ANCOVA with the Baseline duration as a covariate.
  - Null Hypothesis: There is no difference in percent change in time to absence seizure between treatment groups.
  - Alternative Hypothesis: The percent change in time to absence seizure counts differs in at least one treatment group.
- The percent of patients seizure free at Week 4 (Visit 5) defined as having had no absence seizures for all 7 days during the 4th week of the Treatment Period based on seizure diary, will be analyzed to compare doses using Fisher's exact test.
  - Null Hypothesis: There is no difference in percent of seizure free patients between treatment groups.
  - Alternative Hypothesis: There is a significant difference in percent of seizure free patients in at least one treatment group.
- Investigator CGI-I at Week 4 (Visit 5) comparing doses.

  The number of subjects and percentage of subjects within each point along the 7-point scale will be summarized by treatment group for the CGI-I completed by the investigator during Visit 5.

  Change from Visit 3 response will be summarized within treatment groups using descriptive statistics (n, mean, SD, CV%, 90% CIs, median, minimum, and maximum).

  Change in score will be compared between treatment groups using ANCOVA with Visit 3 score as a covariate.
  - Null Hypothesis: The mean CGI-I score does not differ between treatment groups.
  - Alternative Hypothesis: the mean CGI-I score is different in at least one treatment group.

Duration to first absence seizure after initiation of hyperventilation for both Baseline and Week 4 (Visit 5) and change from Baseline will be listed. The average time to first absence seizure after initiation of hyperventilation at Baseline and Week 4 (Visit 5) as well as difference from Baseline at Week 4 (Visit 5) will be summarized and compared by treatment group. The change from Baseline will be summarized by descriptive statistics (n, mean, SD, CV%, 90% CIs, median, minimum, and maximum) and value from the significance testing for the Null hypothesis average difference is equal to 0 vs. Alternative Hypothesis average difference is not equal to 0 will be presented.

Number and percent of patients seizure free vs. not seizure free at visit 5 will be summarized by treatment, and the value from the significance testing will be presented.

CGI-I responses completed by the investigator during Visit 5 will be summarized and presented using a histogram of the number and percentage of each point along the 7-point scale. Visit 3, Visit 5, and change from Visit 3 response will be summarized within treatment groups using descriptive statistics (n, mean, SD, CV%, 90% CIs, median, minimum, and maximum), and the value from the significance testing will be presented.

8.6.3 Exploratory Efficacy Analysis

Time to freedom from seizures will be defined as the Study Day at which no further seizures were recorded for the rest of the Treatment Period.

Number of seizure-free days per week will be defined as the number of days in each Week of Treatment (out of 7) with zero seizures recorded.

Average number of seizures per week will be defined as the total number of seizures in each Week of Treatment, averaged across patients for each treatment group.

Average time to freedom from seizures, number of seizure-free days per week, and number of absence seizures per week (for each of Weeks 1, 2, 3, and 4) will be summarized by treatment group.

No inferential analyses will be conducted for these exploratory efficacy measures.

8.6.4 Methods for Handling Dropouts and Missing Data

Efficacy measures will not be imputed, and patients without a second video-EGG will not be included in analyses requiring the second video-EGG. Patients without a second video-EEG will be included in a sensitivity analysis to assess the impact of excluding missing values versus using imputed values for the final video-EEG as the median of the change from Baseline within treatment group. Impact will be measured as the change in significance in R^2 and/or AIC between the two ANCOVA models.

Missing dates will be imputed as specified in Section 5.8.

8.6.5 Multiplicity

Overall strong type I error control will be achieved for the primary and secondary efficacy endpoints using a fixed sequence closed testing procedure with fallback. Fallback procedures are closed testing procedures that maintain strong control of familywise error rate while allowing testing of all hypotheses even if one or more hypotheses are not rejected earlier in the testing sequence (Wiens and Dmitrienko, 2005)[10]. The primary endpoint and five secondary endpoints are ordered prospectively. In the fixed sequence procedure, each hypothesis is tested, in order, at α = 0.05, until a hypothesis fails to be rejected, after which testing stops. The fallback modification "reserves" a small alpha to be used for the next test in the sequence even if the prior hypothesis is not rejected.

That is, with the hypotheses ordered as $H^1, H^2, \ldots, H^i$, assign α_i' to the i^{th} null hypothesis such that $\sum_{i=1}^{i} \alpha_i' = \alpha$. H^1 is tested at the level $\alpha_i^* = \alpha_i'$. Subsequent hypotheses H^i are tested at the level $\alpha_i^* = \alpha_i'$ if H^{i-1} was not rejected, or $\alpha_i^* = \alpha_i' + \alpha_{i-1}'$ if H^{i-1} was rejected. Specifically, α will be distributed among the hypotheses as α_i' = 0.04, 0.003, 0.002, 0.002, and 0.001, respectively. If H^1 is rejected with $p < 0.04$, H^2 (time to relapse) will be tested at $\alpha_2' = 0.04 + 0.003 = 0.043$. If H^2 is rejected with $p < 0.043$, H^3 is tested at $\alpha_3' = 0.043 + 0.002 = 0.045$, and so on. However, if H^2 is not rejected ($p \geq 0.043$), H^3 is tested at $\alpha_3' = 0.002$.

8.6.6 Pooling of Sites

Data will be pooled across sites for all analyses.

8.7 Safety Analyses

Safety evaluations will be based on the incidence, intensity, type of adverse events (AEs), clinically significant changes in the patient's physical examination findings, electrocardiograms (ECGs), vital sign measurements, and clinical laboratory results.

These analyses will be performed using the Safety population.

No statistical inference is planned.

8.7.1 Adverse Events

Overall summary of TEAE's will be summarized by any TEAE, treatment-related TEAE, treatment-related and severe TEAE, TEAE leading to study drug discontinuation, any serious TEAE, any serious and treatment related TEAE, TEAE resulting in death, and TEAE leading to study discontinuation. Summaries of AEs will include incidence of TEAEs and treatment-related TEAEs by MedDRA preferred term (PT) and system organ class (SOC) by dose cohort. The TEAEs will also be summarized by severity, PT, and SOC by dose cohort.

Missing values for severity will be assigned as "Severe" and missing values for relationship to study treatment will be considered as "Related" in the summary. Subjects reporting more than one TEAE are counted once in each category at the maximum severity.

AEs with a start date during the study will be summarized. Listings of all AEs, AEs leading to discontinuation of the study drug, SAEs, TEAE leading to study discontinuation; and deaths, if any, will be provided.

Adverse events that occur during the video EEG recording will be listed.

Adverse events that occur during the administration of study drug will be listed.

Adverse events that are reported during follow-up phone calls or emails will be listed.

8.7.2 Deaths and Serious Adverse Events

Any SAE, or death related to the study drug will be listed in a table by treatment group.

8.7.3 Laboratory Data

Blood samples will be taken for clinical laboratory tests (chemistry and hematology) and urine will be collected for urinalysis.

The results of the Screening Visit laboratory chemistry, hematology and urinalysis values will be listed and summarized for the Safety Population. Results for subsequent visits will be listed as change from screening per visit, and any change to abnormal status (below LLN or above ULN) and shift tables will be listed and summarized by treatment group. Out of range values as defined by the Central Laboratory will also be listed. If multiple lab values occur on the same date the latest chronological sample per date will be used in the results.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units.

Parameters to be included are:

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC), and platelet count.
- Chemistry: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), lactate dehydrogenase (LDH), uric acid, glucose, and calcium.
- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen.

8.7.4 Vital Signs

Vital signs measurements will be listed and summarized by treatment group for the Safety Population. Results for post Baseline visits will also be listed with change from Baseline per visit.

8.7.5 Physical Examinations, ECGs, and Other Observations Related to Safety

A 12-lead ECG will be completed during Screening and at End of Study or Early Withdrawal. Each ECG will be evaluated for any clinically relevant cardiovascular conditions, defined as any clinically significant abnormalities identified by the reader related to coronary artery disease, coronary spasm, abnormal heart rhythm, hypertrophic cardiomyopathy, heart failure, rheumatic heart disease, or myocarditis, which will be listed and summarized by treatment group.

The following ECG parameters will be captured: HR (Ventricular rate) (beats per minute), PR Interval (msec), QRS Interval (msec), QT Interval (msec), QTcF Interval (msec) [QT interval corrected by Fridericia], RR Interval (msec) and Overall assessment of ECG by the investigator (Normal, Abnormal, Not Clinically Significant (ANCS), Abnormal, Clinically Significant (ACS)).

Abnormal values for QT interval and QTcF will be classified as > 450 msec and > 480 msec, respectively.

ECG parameters will be listed as Baseline values, End of Study/Early Withdrawal values, and change from Baseline. Overall assessment of ECG by the investigator will be listed if there is a change to Abnormal results from Baseline.

The neurological examination includes assessment of mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait, and station as ‘normal’ or ‘abnormal’. Neurological exam results will be listed by Body System for any abnormal findings along with description of any abnormal, clinically significant findings.

A complete physical examination includes assessment of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities as ‘normal’ or ‘abnormal’. Physical exam results will be listed by Body System for any abnormal findings along with description of any abnormal, clinically significant findings.

8.7.6 C-SSRS

For patients aged 7 to 17 years and if the developmental level is appropriate, the Columbia-Suicide Severity Rating Scale (C-SSRS) Children's Version will be utilized to assess suicidality at Screening and End of Study or the Early Withdrawal Visit. For patients who are less than 7 years of age or for whom the

C-SSRS is inappropriate due to the patient's developmental functioning, a clinical assessment will be made. Results of the C-SSRS assessments will be presented in a listing to include outcomes of any clinically relevant findings.

8.8 Pharmacokinetic Analysis

The PK population will be used for PK data analysis. The PK population consists of patients who receive at least one dose of Cannabidiol Oral Solution and have at least one usable CBD plasma concentration measurement. Descriptive statistics of trough plasma concentration and PK parameters data for CBD and 7-OH CBD by Visit, Dose, and Response will be provided.

The following noncompartmental PK parameters will be estimated from the plasma concentration-time data: area under the curve from time 0 to the last measured concentration (AUC0-t) by maximum plasma concentration (Cmax), and time to reach maximum plasma concentration (Tmax) using Phoenix WinNonlin® (Version 7 or higher; Pharsight Corporation, Cary, NC 27518, USA). Additional PK parameters may be estimated, as appropriate. Parameters will be summarized by dose cohort.
Exploratory analysis of dose (exposure)-response relationship will be performed. Further population PK approach may be used for PK parameter estimation, as appropriate.

9.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

10.0 References

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ACS	Abnormal Clinically Significant
AE	Adverse event
AED	Anti-Epileptic Drug
AIC	Akaike Information Criterion
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANCS	Abnormal Not Clinically Significant
ANOVA	Analysis of Variance
AST	Aspartate Transaminase
AUC_{0-t}	Area Under the Concentration-time curve from 0
BID	Bis In Die (twice a day)
BUN	Blood Urea Nitrogen
CAE	Childhood Absence Epilepsy
CBD	Cannabidiol
CGI-I	Clinical Global Impression - Global Improvement
CI	Confidence Interval
C_{max}	maximum plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case Report Form
CTMS	Clinical Trial Management System
C_{trough}	plasma trough concentrations
CV	Coefficient of Variation
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EEG	Electroencephalography
GSW	General Spike Wave
HV	Hyperventilation
IP	Investigational Product
ITT	Intention-to-treat
LDH	Lactate Dehydrogenase

LLN	Lower Limit of Normal
QTcF	QT interval with Fridericia correction
PDI	Dose Intensity
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
R^2	Coefficient of Determination
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
T_{max}	time to maximum concentration
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

Appendix 2 Tables Figures, and Listings

Title	Population
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Table 1.6 Past Medical History by System Organ Class and Preferred Term	(Intent to Treat Population)
Table 1.7.1 Prior Medications by WHO Drug Dictionary Preferred Term	(Intent to Treat Population)
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Table 2.2.1 Summary of Time to First Absence Seizure after Initiation of Hyperventilation Testing Change from Baseline	(Intent to Treat Population)
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Listing 5.2 Demographic and Baseline Data	(Intent to Treat Population)

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Appendix 3 Schedule of Events

ASSESSMENTS	SCREENING PERIOD[a]	TITRATION PERIOD		TREATMENT PERIOD					FOLLOW-UP PERIOD[c]
Visit Number	**1**	**2 Baseline**	**Call/ Email**	**3**	**4**	**5**	**6 End of Study**	**Early Withdrawal Visit[p]**	**7**
Study Time Points	**Days -28 to -1**	**Day 1**	**0-5 or 0-10 days**	**Day 1**	**Week 2**	**Week 4 (Day 6)**	**Week 4 (Day 7)**		**Week 9**
Visit Window (Days)	± 5	± 5		0	0	± 3	± 3	± 5	± 5
Informed consent	X								
Review of inclusion/exclusion criteria	X	X							
Review of historic seizure counts	X								
4-hour video-EEG[d,e]		X[b]				X		X	
Seizure diary[f]	X	X	X	X	X	X		X	
Meal diary[f]		X	X	X		X		X	
Demographics	X								
Assessments of past/current AEDs	X	X	X	X	X	X	X	X	X
Medical Surgical History	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs[g]	X	X		X	X		X	X	
Clinical Laboratory Assessments[h]	X			X	X		X	X	

ASSESSMENTS	SCREENING PERIOD[a]	TITRATION PERIOD		TREATMENT PERIOD					FOLLOW-UP PERIOD[c]
Visit Number	**1**	**2 Baseline**	**Call/ Email**	**3**	**4**	**5**	**6 End of Study**	**Early Withdrawal Visit[p]**	**7**
Study Time Points	**Days -28 to -1**	**Day 1**	**0-5 or 0-10 days**	**Day 1**	**Week 2**	**Week 4 (Day 6)**	**Week 4 (Day 7)**		**Week 9**
Visit Window (Days)	± 5	± 5		0	0	± 3	± 3	± 5	± 5
Concomitant AED levels		X					X	X	
PK Samples				X[i]		X[i]	X[i]	X[j]	
12-lead ECG	X						X	X	
Urine Analysis	X						X	X	
Urine pregnancy screen for post-menarchal females	X								
Physical Examination[k]	X								
Neurological Examination[l]	X	X		X	X		X	X	
Height/Weight	X			X			X	X	
CGI-I				X		X		X	
C-SSRS	X					X		X	
Dosing with Cannabidiol Oral Solution		X[m]	X	X	X	X	X[n]	X[o]	
Drug Accountability			X	X	X		X	X	
AEs	X	X	X	X	X	X	X	X	X

End of Study							X[q]		

[a] Screening should occur within 28 (± 5) days. Patients in Cohort 2 and Cohort 3 may have a waiting period between Screening and Titration Periods while previous Cohort completes the Treatment Period and safety data is reviewed by the DMC.

[b] Patients will have a Baseline 4-hour video EEG (including hyperventilation).

[c] Follow-Up Period Visit (Visit 7) may be a phone call.

[d] Hyperventilation testing will be conducted during the video-EEG.

[e] Patients will return to the study clinic at Visit 5 or the Early Withdrawal Visit for a repeat 4-hour video-EEG.

[f] Seizure diaries will be dispensed during the Screening Visit (Visit 1), reviewed and returned during Visits 2 through 5, and collected during Visit 6. A meal diary will be completed at Baseline (Visit 2); and for 24 hours before each PK sampling visit at Visit 3 and Visit 5 (Week 4, Day 6), or the Early Withdrawal Visit.

[g] Vital signs will be taken after a 5-minute seated rest.

[h] A urine dipstick pregnancy test will be performed on all female post-menarchal patients during Screening (Visit 1).

[i] Blood for pharmacokinetic analyses of CBD and 7-OH CBD will be drawn at Visit 3 (Day 1), Visit 5 (Week 4, Day 6), and Visit 6 (Week 4, Day 7). Blood draws will be taken pre-dose, 2, 4, and 6 hours after the morning dose (but before the next dose). In the Fed state (Visit 5, Week 4 Day 6), pre-dose blood samples should be collected BEFORE dosing with the "high-fat" breakfast (dose will be administered within 30 minutes of start of breakfast). In the Fasted state (Visit 6, Week 4 Day 7), patients will be fasted for 2 hours before the dose.

[j] Trough values of CBD and 7-OH CBD will be collected at the Early Withdrawal Visit prior to dosing.

[k] The physical examination will include evaluation of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities.

[l] A complete neurological exam will be performed during Screening (Visit 1) and brief neurological examination (mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait, and station) will be performed at Visits 2 (Baseline), 3, 4, and 6 (End of Study) or the Early Withdrawal Visit.

[m] Titration dose of study drug will be dispensed after patient qualification.

[n] A risk/benefit assessment will be made and the decision on whether to continue the patient to the long-term safety study will be documented. If patient is not continuing in the safety study, dispense Cannabidiol Oral Solution for Taper Period. Patients who do not choose to enroll in the long-term safety study will taper the dose of Cannabidiol Oral Solution according to the following schedule: doses over 30 mg/kg/day will be reduced to 30 mg/kg/day for five days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for five days and then discontinued; doses between 20-30 mg/kg/day will be reduced to 20 mg/kg/day for five days and then discontinued; doses ≤ 20 mg/kg/day can be discontinued without titration. This can be modified by the investigator based upon the patient's response.

[o] Study drug will be collected but not dispensed.

[p] If the patient withdraws prematurely from the Treatment Period, all Early Withdrawal procedures should be conducted. Site staff will follow up with the patient at 4 weeks after completion of treatment via the telephone to collect information regarding AEs, AEDs, and concomitant medications.

[q] Patients can re-consent to enter the long-term safety study. If patient re-consents, then the patient will continue to receive CBD at their current dose.

AE = adverse event; AED = anti-epileptic drug; CGI-I = Clinical Global Impression – Global Improvement; C-SSRS=Columbia Suicide Severity Rating Scale; EEG = electroencephalography; PK=pharmacokinetics.