STATISTICAL ANALYSIS PLAN
PHASE 3

VERSION: 0.1
DATE OF PLAN:

30 OCT 2017

BASED ON:

INS011-16-082 v2.0
26 Oct 2017

STUDY DRUG:

PROTOCOL NUMBER:

2.0

STUDY TITLE:

A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY, SAFETY, AND TOLERABILITY OF CANNABIDIOL ORAL SOLUTION AS ADJUNCTIVE THERAPY WITH VIGABATRIN AS INITIAL THERAPY IN INFANTS WITH INFANTILE SPASMS

SPONSOR:

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[redacted]

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

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TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company {Sponsor Name}	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Investigational Product: Cannabidiol Oral Solution	**Page:**	
Name of Active Ingredient: Cannabidiol		
Title of Study: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy, Safety, and Tolerability of Cannabidiol Oral Solution as Adjunctive Therapy with Vigabatrin as Initial Therapy in Infants with Infantile Spasms		
Investigators: Approximately 35 sites in the US, Canada, and Australia.		
Studied period (years): Estimated Date of first patient in (FPI): Estimated Date of last patient in (LPI):	**Phase of development: 3**	

Objectives:

Primary:

- To evaluate the efficacy of Cannabidiol Oral Solution as adjunctive therapy with vigabatrin as initial therapy in treating patients with Infantile Spasms.

Secondary

- to evaluate the continued efficacy of the combination treatment of Vigabatrin plus CBD after the initial 14 days.
- To evaluate the safety and tolerability of Cannabidiol Oral Solution as adjunctive therapy with vigabatrin as initial therapy in treating patients with Infantile Spasms.

Methodology:

This is a Phase 3, double-blind, placebo-controlled, randomized, multicenter study to evaluate the efficacy, safety, and tolerability of Cannabidiol Oral Solution (CBD) as adjunctive therapy with Vigabatrin as initial therapy, compared to Vigabatrin alone in the treatment of infants newly diagnosed with Infantile Spasms (IS). Randomization will be stratified by developmental impairment (high or low) as determined by the investigator during Screening Visit 1 and then allocated to one of two treatment groups:

- Treatment with vigabatrin *plus*
  - CBD 40 mg/kg/day, or
  - Matching CBD 40 mg/kg/day placebo

One hundred eighty patients in total will be enrolled into one of the two treatment arms: 120 patients in the investigational product arm and 60 patients in the placebo arm. Patients will be dosed approximately every 12 hours with food to help ensure consistent plasma levels are achieved.

In addition to the safety assessments required by the study protocol, the investigator will monitor patients throughout the study as recommended in the current approved product label for Vigabatrin. Study participants will be newly diagnosed pediatric patients age 3 to 12 months (inclusive) experiencing infantile spasms who satisfy all inclusion/exclusion criteria. This study will be comprised of five periods: Screening, Initial Treatment, Extended Treatment, Taper, and Follow-up Periods, with a maximum duration of approximately 137 days.

Each newly diagnosed patient with Infantile Spasms will complete a Screening Period for up to 14 (± 5) days.

Patients will have an overnight, minimum of a 9-hour video-EEG that includes at least one full sleep-wake cycle during their Screening Visit to establish their baseline level of infantile spasms and hypsarrythmia or a pattern of epileptic encephalopathy, and a 24-hour video-EEG at Visit 4 (Day 13) of the Initial Treatment Period to establish their final level of infantile spasms and hypsarrythmia. During the Extended Treatment Period, a 9-hour video-EEG will be conducted to confirm parent/caregiver report of relapse or resolution.

<u>Initial Treatment Period</u>

At the Baseline Visit (Visit 2, Day 1), patients will receive the titration dose of Vigabatrin (50 mg/kg/day divided twice daily [BID]), and either CBD 20 mg/kg/day plus matching CBD 20 mg/kg/day placebo or CBD 40 mg/kg/day placebo, each drug administered twice daily for three days.

On Day 4 (Visit 3), patients will return to the study center to evaluate medical status (seizure diary, vital signs, and neurological exam), clinical laboratory assessments, and assess adverse events (AEs), then increase Vigabatrin to 100 mg/kg/day, and CBD or matching CBD placebo to 40 mg/kg/day for 11 days. Vigabatrin, CBD, and matching placebo will be administered in a twice daily fashion at 12-hour intervals. As part of their standard of care, the investigator will assess safety and tolerability during the first three days of the Initial Treatment Period.

Patients will be dosed for a total of 14 days during which the investigator will assess tolerability and efficacy.

Extended Treatment Period

Following the Initial Treatment Period, Complete and Partial Responders in the treatment arm will continue receiving CBD 40 mg/kg/day and Vigabatrin for 76 days, until Week 13 (Day 90) to monitor progress for treatment response. Complete and Partial Responders in the placebo arm will continue receiving Vigabatrin during the Extended Treatment Period. Non-responders will be tapered off Vigabatrin and CBD as specified in the Protocol.

Taper Period

Following the completion of the Initial Treatment Period (Visit 5), all non-responders receiving Vigabatrin will be tapered off. Similarly, all non-responders receiving CBD will be tapered off according to the protocol. Patients will also be tapered off Vigabatrin and CBD at the completion of the Extended Treatment Period or at Early Withdrawal Visits.

Follow-up Period

A follow-up phone call will occur 30 days after discontinuation of the study drug to assess AEs, AEDs, and record concomitant medications.

Study Assessments

To assess efficacy, a 9-hour video-EEG that includes at least one sleep-wake cycle, a 24-hour video-EEG, daily seizure diaries, and investigator Clinical Global Impressions-Global Improvement (CGI-I) assessments will be completed and evaluated.

- A 9-hour video EEG that includes at least one sleep-wake cycle will be completed during Screening (Visit 1) and a 24-hour video EEG will be completed at Visit 5.
- Daily seizure diaries will be completed throughout the Initial and Extended Treatment Periods. The daily record will ask: “How many spasms did the patient have today?”
- The CGI-I will be completed by the investigator at Visit 5 of the Initial Treatment Period, or at Early Withdrawal.

Safety assessments for all patients will include medical history, physical examination, vital signs (seated blood pressure, pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, and urinalysis), prior medication history (assessment of past/current AEDs and concomitant medications), and AE assessments will be conducted at specific visits throughout the study.

If a patient discontinues the study prematurely, the parent’s impression of efficacy and tolerability of the study drug, as evaluated by CGI-I, will be assessed and recorded immediately before discontinuation. If possible, the parent/caregiver will be encouraged to have the patient have an Early Withdrawal video-EEG completed.

Number of patients (planned):

Approximately 180 patients (120 patients in the active drug arm and 60 patients in the placebo arm).

Diagnosis and main criteria for inclusion: Patients will be male and female patients between 3 and 12 months of age (inclusive), with a new clinical diagnosis of Infantile Spasms, confirmed by video-EEG analysis during the Screening Period, have adequate renal and hepatic function and who meet all the inclusion and none of the exclusion criteria. Parent(s)/caregiver(s) must be able to understand and provide written consent.
Investigational product, dosage, and mode of administration: Cannabidiol Oral Solution or Placebo (IP). Initial dose of the IP will be either matching CBD placebo 20 mg/kg/day or CBD 20 mg/kg/day for 3 days, after which the dose of IP will be adjusted to the final dose of CBD or CBD placebo 40 mg/kg/day divided twice daily for 11 days, manufactured for and supplied by Insys Development Company, Inc. Following the completion of the 14-day Initial Treatment Period, Complete and Partial Responders will receive CBD 40 mg/kg/day for 76 days during the Extended Treatment Period.
Duration of treatment: The maximum duration of the study from screening to follow-up of AEs will be approximately 144 days.
Reference therapies, dosage and mode of administration: Vigabatrin powder suspension divided twice daily with food, 50 mg/kg/day for 3 days, then 100 mg/kg/day for 11 days.

Criteria for evaluation:

Efficacy

Primary efficacy endpoint

- Percent of patients who are considered complete responders, defined as complete resolution of spasms and hypsarrhythmia or a pattern of epileptic encephalopathy confirmed by 24-hour video-EEG from Day 13 to Day 14, as determined by the Independent Central Reader.

Secondary efficacy endpoints

- Percent of patients with resolution of infantile spasms as assessed by 24-hour video-EEG from Day 13 to Day 14 (partial response).
- Percent of patients with resolution of hypsarrhythmia or pattern of epipleptic encephalopathy as assessed by 24-hour video-EEG from Day 13 to Day 14 (partial response).
- Investigator impression of efficacy and tolerability of study drug (CGI-I) at Visit 5 (End of Study) or Early Withdrawal.
- Percent reduction in spasm-free days between the Initial Treatment Period (Days 1 to 14) and Screening Period (Days -14 to -1), as determined by the seizure diary entries.
- For patients with a complete response during the Initial Treatment Period who continue: percent of patients who relapse during the Extended Treatment Period confirmed by video-EEG following parent report of relapse, and time to relapse.
- For patients with partial response during the Initial Treatment Period who continue: percent of patients who achieve complete response during the Extended Treatment Period, confirmed by video-EEG following parent report, and time to complete response.

Safety

The safety endpoints of the study are the incidence of treatment-emergent AEs (TEAEs), clinical laboratory assessments, vital signs (blood pressure, pulse rate, respiration rate, and temperature), physical and neurological examination assessments, prior and concomitant medications.

Pharmacokinetic

Trough concentrations (Ctrough) of cannabidiol (CBD) and metabolite 7-hydoxy-CBD (7-OH-CBD) will be used to assess the exposure-response relationship.

Statistical methods:

Sample Size Calculation

A total of 180 patients (120 and 60 patients in the two groups) will provide 80% power with a two-sided alpha of 0.05 to detect a difference in response rate, assuming the response with vigabatrin alone is 40% and the response with vigabatrin with Cannabidiol Oral Solution is 62%.

Analysis Populations

Statistical analyses will be conducted on the following populations:

- Safety Population: The Safety Population will include all patients who were treated with at least one dose of the study drug.
- Intent to Treat (ITT) Population: The ITT Population will include all patients who were randomized.

Efficacy Analyses

The ITT Population will be used for all efficacy analyses.

- For the primary endpoint, a 2-sided Type I error rate of 0.05 will be used.
- For the secondary efficacy endpoints, to maintain the trial-wise Type I error rate at 0.05, False Discovery Rate multiple comparisons correction will be used.
- For endpoints that are continuous in nature, the number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive statistics. For inferential statistics, a t-test or ANCOVA will be used to compare treatment to placebo group.
- For endpoints that are categorical in nature, frequency, counts, and percentages will be presented as descriptive statistics, and Fisher's exact test, Cochran-Maentel-Haenzel, or logit model will be used for inferential statistics as appropriate.

<u>Primary Efficacy Analysis</u>

- Percent of patients with resolution of both infantile spasms and hypsarrhythmia or a pattern of epileptic encephalopathy at Day 14 (complete response) will be compared between Vigabatrin plus Placebo and Vigabatrin plus CBD 40 mg/kg/day groups using Fisher's exact test.

<u>Secondary Efficacy Analyses</u>

- Percent of patients with resolution of infantile spasms at Day 14 will be compared between treatment groups using Fisher's exact test.
- Percent of patients with resolution of hypsarrhythmia or a pattern of epileptic encephalopathy at Day 14 will be compared between treatment groups using Fisher's exact test.
- Investigator impression of efficacy and tolerability of study drug (Clinical Global Impression – Global Improvement (CGI-I) will be compared between treatment groups using a t-test.

- Percent reduction in spasm-free days between the Initial Treatment Period (Days 1 to 14) and Screening Period (Days -14 to -1) will be compared between treatment groups using ANCOVA with the baseline score as a covariate.
- Percent of patients who relapse during the Extended Treatment Period will be compared between 14-day Vigabatrin + CBD responders and 14-day Vigabatrin + placebo responders using Fisher's exact test. Time to relapse will be calculated with Kaplan-Meier curves and compared using a log-rank test.
- Percent of patients with partial response at Day 14 who achieve complete response during the Extended Treatment Period will be compared using Fisher's exact test. Time to complete response will be calculated with Kaplan-Meier curves and compared using a log-rank test.

Safety Analyses

The Safety Population will be used for all safety assessments. All safety assessments will be descriptive and no inferential statistics are planned for safety assessments. All data listings will be provided for protocol specified safety data.

- The Medical Dictionary for Regulatory Activities (MedDRA; Version 20.0 or higher) will be used to classify all adverse events with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs by treatment group.
- Clinical laboratory findings will be summarized for all patients in the safety population for observed values and change from baseline. Shifts from baseline to outside normal range criteria will also be presented for all patients in the safety population.
- Vital signs will be summarized for all patients in the safety population for observed values and change from baseline as appropriate.
- The neurological examination results will be listed and summarized descriptively. Shifts from baseline according to normal and abnormal criteria will also be presented for all patients in the safety population.
- Results of physical examinations conducted throughout the study will be presented in listings and summarized descriptively. Shifts from baseline according to normal and abnormal criteria will also be presented for all patients in the safety population.
- Prior medication and concomitant medications will be reported in the data listings.
- Statistical analyses will be performed using SAS® (Version 9.3 or higher, SAS Institute Inc.) or R (Version 3.3 or higher, Roswell Park Cancer Institute).

Pharmacokinetic Analyses

Exploratory analyses of dose (exposure)-response relationship will be performed. Further population PK approach may be used for PK parameter calculations, as appropriate.

Missing Data

There will be no imputation of the missing values. All assessments will be conducted based on all observed data. A sensitivity analysis may be conducted to assess the impact of the missing values on the final analysis. The sensitivity analyses will be detailed in the SAP.

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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation or Specialist Term	Explanation
AE	adverse event
AED	anti-epileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Global Improvement
cGMP	current Good Manufacturing Practices
C_{trough}	plasma trough concentrations
CRF	case report form
CRO	contract research organization
CV%	coefficient of variation
CYP	cytochrome P450
CYP1A1	Cytochrome P450 1A1
CYP2C19	Cytochrome P450 2C19
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytochrome P450 3A4
CYP3A5	Cytochrome P450 3A5
DEA	Drug Enforcement Administration
DMC	Data Monitoring Committee
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EEG	electroencephalogram
EENT	eyes, ears, nose, and throat
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IA	Interim Analysis
IB	Investigator's Brochure
ICF	informed consent form
ICD	informed consent document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IS	Infantile Spasms
ITT	Intent to Treat
LFTs	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No Observed Adverse Effect Level
OH	hydroxy
PK	pharmacokinetic(s)
PT	preferred term
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
VNS	vagus nerve stimulation

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol INS011-16-082.

Protocol Revision Chronology:		
INS011-16-082	30 Oct 2017	V2.0

This SAP was developed per guidance documents ICH E9, Statistical Principles for Clinical Trials-v1.0. and ICH E9(R1): Addendum to Statistical Principles for Clinical Trials Final Concept Paper.

All decisions regarding final analysis, as defined in this SAP, will be made prior to Database Lock (unblinding) of the study data. Further information can be found in the protocol.

The statistical analysis plan (SAP) is based on:

- Protocol No. INS011-16-082, dated October 30, 2017.
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials).
- 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. INS011-16-082.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before the database is locked. Deviations from the final approved plan will be noted in the clinical study report.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the efficacy of Cannabidiol Oral Solution as adjunctive therapy with vigabatrin as initial therapy in treating patients with Infantile Spasms.

2.2. Secondary Objectives

- to evaluate the continued efficacy of the combination treatment of Vigabatrin plus CBD after the initial 14 days.
- To evaluate the safety and tolerability of Cannabidiol Oral Solution as adjunctive therapy with vigabatrin as initial therapy in treating patients with Infantile Spasms.

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 3, double-blind, placebo-controlled, randomized, multicenter study to evaluate the efficacy, safety, and tolerability of Cannabidiol Oral Solution (CBD) as adjunctive therapy with Vigabatrin as initial therapy, compared to Vigabatrin alone in the treatment of infants newly diagnosed with Infantile Spasms (IS). Randomization will be stratified by developmental impairment (high or low) as determined by the investigator during Screening Visit 1 and then allocated to one of two treatment groups:

- Treatment with Vigabatrin plus
    - CBD 40 mg/kg/day, or
    - Matching CBD 40 mg/kg/day placebo

One hundred eighty patients in total will be enrolled into one of the two treatment arms: 120 patients in the investigational product arm and 60 patients in the placebo arm. Patients will be dosed approximately every 12 hours with food.

Study participants will be newly diagnosed pediatric patients age 3 to 12 months (inclusive) experiencing infantile spasms who satisfy all inclusion/exclusion criteria. This study will be comprised of five periods: Screening, Initial Treatment, Extended Treatment, Taper, and Follow-up Periods, with a maximum duration of approximately 137 days.

Each newly diagnosed patient with Infantile Spasms will complete a Screening Period for up to 14 (± 5) days.

Patients will have an overnight, minimum of a 9-hour video-EEG that includes at least one full sleep-wake cycle during their Screening Visit to establish their baseline level of infantile spasms and hypsarrythmia or a pattern of epileptic encephalopathy, and a 24-hour video-EEG at Visit 4 (Day 13) of the Initial Treatment Period to establish their final level of infantile spasms and hypsarrythmia. During the Extended Treatment Period, a 9-hour video-EEG will be conducted to confirm parent/caregiver report of relapse or resolution.

<u>Initial Treatment Period</u>

At the Baseline Visit (Visit 2, Day 1), patients will receive the titration dose of Vigabatrin (50 mg/kg/day divided twice daily [BID]), and either CBD 20 mg/kg/day plus matching CBD 20 mg/kg/day placebo or CBD 40 mg/kg/day placebo, each drug administered twice daily for three days.

On Day 4 (Visit 3), patients will return to the study center to evaluate medical status (seizure diary, vital signs, and neurological exam), clinical laboratory assessments, and assess adverse events (AEs), then increase Vigabatrin to 100 mg/kg/day, and CBD or matching CBD placebo to 40 mg/kg/day for 11 days. Vigabatrin, CBD, and matching placebo will be administered in a twice daily fashion at 12 hour intervals. As part of their standard of care, the investigator will assess safety and tolerability during the first three days of the Initial Treatment Period. Patients

will be dosed for a total of 14 days during which the investigator will assess tolerability and efficacy.

Extended Treatment Period

Following the Initial Treatment Period, Complete and Partial Responders in the treatment arm will continue receiving CBD 40 mg/kg/day and Vigabatrin for 76 days, until Week 13 (Day 90) to monitor progress for treatment response. Complete and Partial Responders in the placebo arm will continue receiving Vigabatrin during the Extended Treatment Period. Non-responders will be tapered off Vigabatrin and CBD as specified in the Protocol.

Taper Period

Following the completion of the Initial Treatment Period (Visit 5), all non-responders receiving Vigabatrin will be tapered. Similarly, all non-responders receiving CBD will be tapered off according to the protocol. Patients will also be tapered off Vigabatrin and CBD at the completion of the Extended Treatment Period or Early Withdrawal Visits.

Follow-up Period

A follow-up phone call will occur 30 days after discontinuation of the study drug to assess AEs, AEDs, and record concomitant medications.

Study Assessments

To assess efficacy, a 9-hour video-EEG that includes at least one sleep-wake cycle, a 24-hour video-EEG, daily seizure diaries, and investigator Clinical Global Impressions-Global Improvement (CGI-I) assessments will be completed and evaluated.

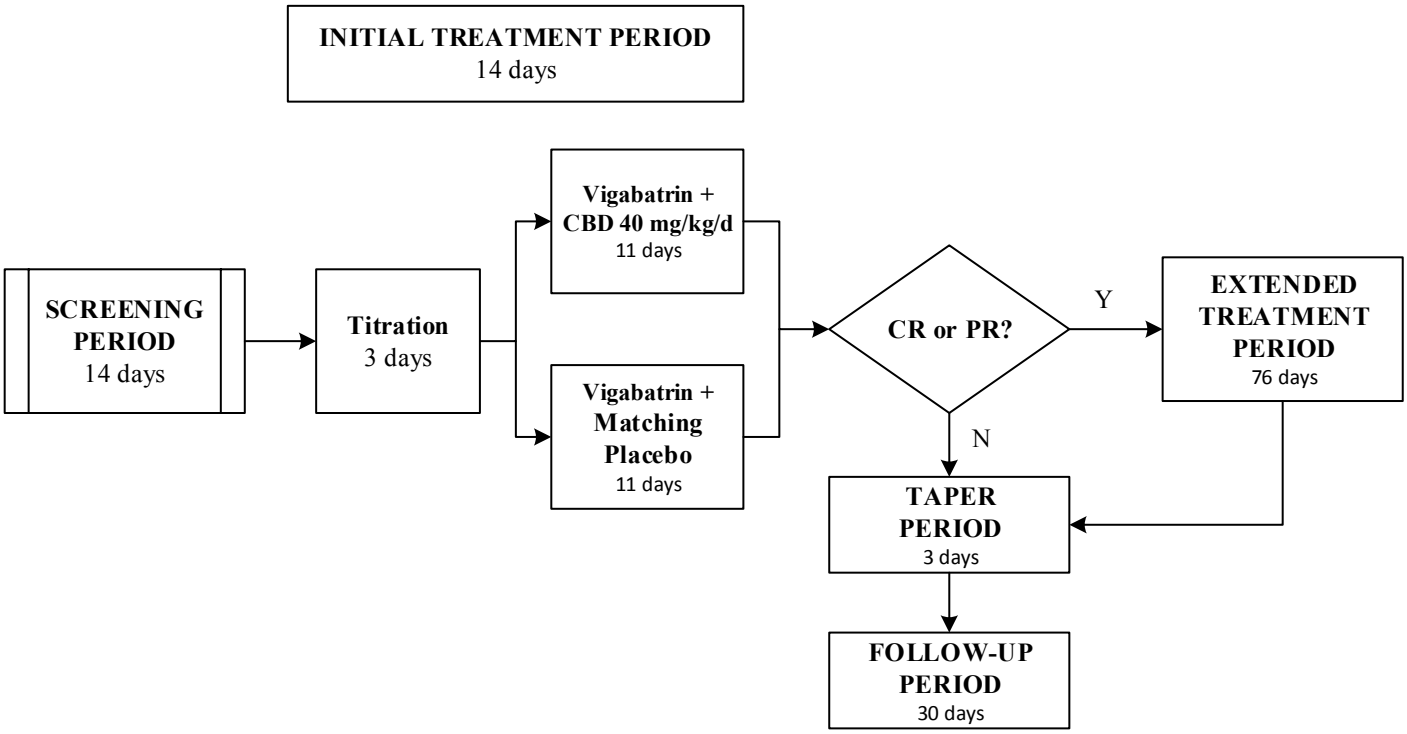
- A 9-hour video EEG that includes at least one sleep-wake cycle will be completed during Screening (Visit 1), and a 24-hour video EEG will be completed at Visit 5.
- Daily seizure diaries will be completed throughout the Initial and Extended Treatment Periods. The daily record will ask: “How many spasms did the patient have today?”
- The CGI-I will be completed by the investigator at Visit 5 of the Initial Treatment Period, or at Early Withdrawal.

Safety assessments for all patients will include medical history, physical examination, vital signs (seated blood pressure, pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, and urinalysis), prior medication history (assessment of past/current AEDs and concomitant medications), and AE assessments will be conducted at specific visits throughout the study.

If a patient discontinues the study prematurely, the parent’s impression of efficacy and tolerability of the study drug, as evaluated by CGI-I, will be assessed and recorded immediately

before discontinuation. If possible, the parent/caregiver will be encouraged to have the patient have an Early Withdrawal video-EEG completed.

Figure 1: Study Design Schematic



CR = complete responder; PR = partial responder

3.2. Selection of Study Population

3.2.1. Inclusion Criteria

Diagnosis and main criteria for inclusion:

Patients will be male and female patients between 3 and 12 months of age (inclusive), with a new clinical diagnosis of Infantile Spasms, confirmed by video-EEG analysis during the Screening Period, have adequate renal and hepatic function and who meet all the inclusion and none of the exclusion criteria. Parent(s)/caregiver(s) must be able to understand and provide written consent.

All patients must satisfy the following criteria to be considered for study participation:

1. Parent(s)/caregiver(s) fully comprehend and sign the informed consent form, understand all study procedures, and can communicate satisfactorily with the investigator and study coordinator, in accordance with applicable laws, regulations, and local requirements.
2. Male or female between 3 months to 12 months of age (inclusive) at time of consent.
3. Clinical diagnosis of infantile spasms, confirmed by video-EEG analysis (including at least one cluster of electroclinical spasms [≥3 in any 10-minute epoch)], hypsarrythmia or a pattern of epileptic encephalopathy) obtained during the Screening Period and read by the Investigator.
4. General good health (defined as the absence of any clinically relevant abnormalities as determined by the investigator) based on physical and neurological examinations, medical history and clinical laboratory values completed during the Screening Visit (Visit 1).
5. In the opinion of the investigator, the parent(s)/caregiver(s) is (are) willing and able to comply with the study procedures and visit schedules.

3.2.2. Exclusion Criteria

Patients will be excluded for any of the following:

1. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator's Brochure for Cannabidiol Oral Solution) to be an unsuitable candidate to receive the study,
2. Known or suspected allergy to Cannabidiol Oral Solution.
3. History of an allergic reaction or a known or suspected sensitivity to any substance that is contained in the investigational product formulation.
4. Use of any cannabidiol/cannabis product within 30 days of study entry.
5. Patient is diagnosed or at high risk of having tuberous sclerosis.
6. Patient has received treatment with either vigabatrin, ACTH, or high-dose steroids previously.
7. Previous or concomitant therapy with felbamate, clobazam, valproic acid, or the ketogenic diet.
8. Positive drug screen for THC.
9. Patient currently on any disallowed CYP3A4-related medication listed in Appendix 1 of the protocol (phenytoin, fluvoxamine, carbamazepine, and St. John's Wort).
10. Previously received any investigational drug or device or investigational therapy within 30 days before Screening.

11. Clinically significant abnormal laboratory values, including: liver function tests (LFTs) such as albumin, direct bilirubin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN).
12. The investigator may deem the patient eligible if he or she judges the laboratory values to be not clinically significant.

3.3. Sample Size Calculation

A total of 180 patients (120 patients in the 40 mg/kg/day arm and 60 patients in the placebo arm) will provide 80% power with a two-sided alpha of 0.05, assuming the response with vigabatrin alone is 40% and the response with vigabatrin with Cannabidiol Oral Solution is 62%.

4. STUDY DURATION AND VISIT SCHEDULE

This study will be comprised of 5 periods: a Screening Period (up to 14 days), Initial Treatment Period (14 days), Extended Treatment Period (9 weeks), a Taper Period (3 days) for patients who elect not to enroll in the open-label long-term safety study, and a Follow-up Period (30±7 days). The maximum study duration is expected to be approximately 144 days.

4.1. Screening Period (Visit 1)

The following screening procedures and assessments are intended to be performed during Visit 1, but the patient may return to complete activities, which must be performed within 14 days of the start of the Initial Treatment Period for all patients: written informed consent is obtained and inclusion and exclusion criteria reviewed, demographic data, recent concomitant medication and procedures, medical and surgical history, seizure frequency history occurring ≤28 days of the Screening Visit, patient risk of developmental impairment, adverse events (AEs), and vital signs (blood pressure, pulse rate, respiratory rate, and temperature measurements) will be recorded.

Urine (for urinalysis) and blood samples (for hematology, chemistry, and drug screen) will be obtained.

A complete physical examination (including height, weight, and head circumference) and brief neurological examination will be performed.

A 9-hr video-EEG (includes a full sleep-wake cycle) and a daily seizure diary will be provided.

4.2. Initial Treatment Period (Visits 2, 3, 4, and 5)

4.2.1. Visit 2 (Day 1)

During Visit 2, the patient will be randomized and receive the titration doses of Vigabatrin and CBD or matched placebo. AEs will be recorded.

4.2.2. Visit 3 (Day 4)

During Visit 4, a brief neurological examination will be performed and blood samples will be taken for hematology and chemistry. The following assessments will be recorded: height and weight, vital signs, concomitant medications and procedures, AEs, and daily seizure diary.

The patient will have their full study dose of Vigabatrin and CBD or matched placebo dispensed and the morning dose of the investigational product will be administered. After administration of the morning dose, the patient will remain at the study center for 4 hours. Additional brief neurological examinations will be performed at 2 and 4 hours postdose, and vital signs will be recorded at 4 hours postdose. AEs and SAEs will be recorded.

4.2.3. Visit 4 (Day 13)

On Day 13, patients will be admitted to the study center before the morning administration of the investigational product. The following assessments will be completed PRIOR to administration of the morning dose of the investigational product: record concomitant medications and procedures, vital signs, height and weight, draw blood samples, brief neurological examination, AEs, and daily seizure diary.

The morning dose will be administered following the assessments listed above, AEs will be recorded, and the 24-hour video-EEG assessment will be started.

4.2.4. Visit 5 (Day 14)

The following activities will occur on Day 14, at approximately 24 hours post the Day 13 morning dose: finish the 24-hour video-EEG assessment; assessment of current AEDs, record concomitant medications and procedures, vital signs, height and weight, review daily seizure diary, and AEs; draw blood samples (for hematology, chemistry and PK), perform a brief neurological examination, and completion of investigator CGI-I.

4.3. Extended Treatment Period (Week 6, Week 10, and Week 13)

Following the Initial Treatment Period, Complete and Partial Responders will continue receiving CBD 40 mg/kg/day and/or vigabatrin for 76 days, until Week13 (Day 90).

The following assessments and procedures will be completed at Visit 6 (Week 6), Visit 7 (Week 10), and Visit 8 (End of Study; Week 13): record concomitant medications and procedures, vital signs, AEs, and review daily seizure diary; draw blood samples for hematology and chemistry; perform a brief neurological examination, and complete the investigator CGI-I.

In addition, a 9-hour video-EEG will be performed to confirm parent/caregiver report of relapse. All patients will begin tapering off CBD and Vigabatrin at the end of this period.

4.4. Early Withdrawal Visit

Should a patient's participation be terminated prior to Day 14 or Day 90 for any reason, an Early Withdrawal Visit will be completed. The following procedures will be completed: record concomitant medications and procedures, vital signs, height and weight, review daily seizure diary, and AEs; draw blood samples for hematology and chemistry; perform a brief neurological examination; perform a 9-hour video-EEG (if possible) and complete investigator CGI-I.

All patients will begin tapering off CBD and Vigabatrin at this visit.

4.5. Follow-up Period

A follow-up phone call will occur 30 days after discontinuation of the study drug to assess AEs, AEDs, and record concomitant medications.

5. CLINICAL ASSESSMENTS

5.1. Demographics and Medical History

The Investigator or designee will record the following information during the Screening Period: demographic data, including *sex, date of birth, race, ethnicity, medical history, medications history,* and *concomitant medications*.

5.2. Efficacy Assessments

5.2.1. Video-EEG

Video-EEGs performed during the Screening Visit and Visit 4 to Visit 5 (Day 13 and Day 14), and during the Extended Treatment Period to confirm parent reports of relapse or seizure cessation. Data collected include: *Presence of spasms (Y/N), Number of spasms,* and *presence of Hypsarrhythmia (Y/N), presence of epileptic encephalopathy (Y/N)*.

5.2.2. CGI-I

Clinical Global Impression of Improvement (CGI-I) will be completed by the investigator at Visit 5 (Treatment Period Day 14). CGI-I will be completed by the investigator, if possible, during the Early Withdrawal Visit or by the parent is a Visit is not completed.

The CGI-I assessment for each subject will also be a scale of 1 to 7:

- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse.

5.2.3. Seizure Diary

The seizure diary records the date, the number of spasms observed each day, and current dose of medications.

5.3. Safety Assessments

5.3.1. Physical Examination

The physical examination during the Screening Visit will include evaluation of *general appearance, ears, eyes, nose, and throat (EENT), heart, peripheral vasculature, lungs,*

musculoskeletal system, abdomen, neurologic function, endocrine system, and *skin,* assessed as 'normal' or 'abnormal'. *Height/length* and *weight* will be obtained.

5.3.2. Neurological Examinations

The brief neurological examination will assess *mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait,* and *station* (normal/abnormal).

5.3.3. Vital Signs

Vital signs will consist of seated or supine *blood pressure* (depending on patient age and ability), *pulse rate, temperature*, and *respiration rate* measurements. The most recent valid measurement prior to first dose of study medications will be defined as the Baseline measure.

5.3.4. Clinical Laboratory Assessments

Blood samples will be collected during the Screening Visit and Visits 3 through 8, and at the Early Withdrawal Visit.

5.3.4.1. Hematology

Blood samples for the following hematology assessments will be collected: *hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC),* and *platelet count.*

5.3.4.2. Chemistry

Blood samples will be collected for the following serum chemistry assessments: *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.*

5.3.4.3. Drug Screen

A blood sample will be collected during the Screening Visit for a drug screen, which will test for presence of *amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, morphine, 3,4-methylenedioxymethamphetamine (ecstasy), THC, phencyclidine, cotinine, alcohol,* and *opiates.*

5.3.4.4. Urinalysis

Urine will be collected during the Screening Visit for the following urinalysis assessments: *pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase,* and *urobilinogen.*

6. DEFINITIONS AND CONVENTIONS

6.1. General Summary Table and Individual Subject Data Listing Considerations

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

A patient's Baseline value will be the last measurement taken prior to treatment. For any variable with Change From Baseline (CFB) calculated, CFB will be calculated as:

CFB = Post-Baseline value - Baseline value.

6.2. Calculations Using Dates

Age will be calculated as:

Age = Integer((Date of enrollment – Date of Birth)/365.25)

Study Day will be calculated as

Study Day = Integer(Date of Event - Day 1 of Treatment) + 1

6.3. Baseline

The Baseline value for any measurement will be the most recent valid value prior to the first dose of study medication.

6.3.1. Visit Windows Relative to the First Dose of Study Medication

Table 2: Visit windows and target days

Visit	Relative Target Day	Visit Window
Visit 1 (Screening)	-14	-14 – -1
Visit 2	Day 1	1
Visit 3	4	4
Visit 4	13	13
Visit 5 (End of Study)	14	14
Visit 6	Week 6	
Visit 7	Week 10	
Visit 8 (End of Study)	Week 13	
Early Withdrawal		
Taper Period		3 days
Followup Period		30 days

6.4. Analysis Populations

6.4.1. Safety Population

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

6.4.2. Intent to Treat Population

The Intent to Treat (ITT) Population will include all subjects who randomized. The ITT will be used for all efficacy assessments.

6.4.3. PK Analysis Population

The PK Analysis Population will include all subjects who were treated with at least one dose of the study drug and have at least one usable plasma concentration measurement.

6.4.4. Handling of Missing Values

There will be no imputation of the missing values. All assessments will be conducted based on all observed data. A sensitivity analysis will be conducted to assess the impact of the missing values on the final analysis.

Partial missing dates will be imputed as described in Table 3. 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.

Table 3: Calculation of missing or partially missing dates

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		

7. DATA PRESENTATIONS AND DATA MANAGEMENT

7.1. Data Presentations

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided.

7.2. Data Management

Data management for this study will be the responsibility of the CRO as described in the Data Management Plan.

7.3. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

8. PATIENT DISPOSITION AND PROFILE OF SCREEN FAILURES

The number of patients in the ITT and Safety Analysis Population will be summarized along with reasons for early discontinuation from the study. 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.

Discontinuation reasons are as follows:

- Inadvertently enrolled (enrollment criteria not met)
- Investigator decision
- Adverse Event
- Subject withdrew consent
- Lack of protocol compliance
- Subject attempted suicide or is at risk of suicide
- Sponsor decision
- Subject becomes pregnant
- Abnormal laboratory values
- Lost to follow-up
- Death
- Other

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

- Administrative Criteria
- Eligibility and Entry Criteria
- IP Compliance
- Informed Consent
- Laboratory Assessment Criteria
- Serious AE Criteria
- Study Procedures Criteria
- Regulatory or Ethics Approvals Criteria
- Visit Scheduled Criteria
- Other Criteria

Supportive listings will also be provided:

- Allocation to treatment
- Protocol deviations
- Subjects eligibility criteria

8.1. Patient Accounting

Patients who are randomized will be listed and summarized including number of patients randomized (ITT), treated (Safety Population), in PK Population, and number and reason for discontinuation.

8.1.1. Patient Accounting by Treatment Group

Patients who are randomized will be listed and summarized by treatment group including number of patients randomized (ITT Population), treated (Safety Population), in PK Population, and number and reason for discontinuation.

8.1.2. Patient Distribution by Investigator

Patients who are randomized will be listed and summarized by investigator, including number of patients randomized (ITT Population), treated (Safety Population), in PK Population, and number and reason for discontinuation.

8.2. Screen Failure

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

9. BASELINE SUBJECT DATA

9.1. Baseline Demographic and Physical Characteristics

Demographic and baseline characteristics (including age in months, gender, race, ethnicity, length, weight, BMI, head circumference, video-EEG results) will be summarized for both the Safety and ITT Populations. All demographic and baseline characteristics along with body mass index (BMI) will be listed for the Safety Population.

9.2. Medical History and Medical Conditions Present at Entry

Medical and surgical history will be coded using the MedDRA, version 20.0 or above, and will be summarized by system organ class and preferred term for the Safety Population.

Development will be summarized as 'high' or 'low' risk of developmental impairment as defined by the International Collaborative Infantile Spasms Study (ICISS) for the Safety Population. ICISS criteria include the presence or absence of the following factors that increase the risk of developmental impairment: chromosomal abnormality or clinical syndrome, neonatal encephalopathy with seizures, and cerebral palsy or developmental impairment diagnosed before onset of spasms.

9.3. Prior Medication History and Medications Present at Entry

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD), version March 2017 and will be summarized separately by preferred term for the Safety Population. The details of medication and foods excluded from the study are presented in the protocol. At each level of summarization, subjects reporting more than one medication will be counted only once.

Summary tables and listings will include Baseline assessment data.

9.3.1. Non-Diagnosis Related Prior Medication History

Prior non-diagnosis related medications are classified as medications which stopped before the date of first dose of study medication while concomitant medications are medications started prior to, on or after the first dose of study medication, and ended on or after the date of first dose of study medication or were ongoing at the end of the study. At each level of summarization, subjects reporting more than one medication will be counted only once. Summary tables and listings will include Baseline assessment data.

9.3.2. Prior Diagnosis Related Medication History

Patients with prior anti-epileptic drug administration will be excluded from this study.

9.3.3. Missing and Partially Missing Start and Stop Dates

Imputation of missing dates is described in Section 6.4.4.

9.4. Baseline Physical Examination

Results of the Screening Visit complete physical examination will be listed and summarized by treatment group for both the Safety and Efficacy Population. General appearance, ears, eyes, nose, and throat (EENT), heart, peripheral vasculature, lungs, musculoskeletal system, abdomen, neurologic function, endocrine system, and skin will be assessed and summarized as 'normal' or 'abnormal'. Height/length and weight will be summarized and BMI calculated.

9.5. Baseline Vital Signs

Baseline Vital Signs will be defined as the most recent valid measurement taken before receiving the first dose of medication during Visit 3 (Treatment Period Day 1). Vital signs will be summarized for both the Safety and ITT Population. Vital signs will consist of blood pressure, pulse rate, temperature, and respiration rate measurements.

9.6. Baseline Laboratory Data

Results of the Screening Visit laboratory values will be summarized for both the Safety and ITT Population. 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.

The results of the Screening Visit drug screen will be listed for the Safety Population, to include amphetamines, barbiturates, tricyclic antidepressants, cocaine, methadone, morphine, 3,4-methylenedioxymethamphetamine (ecstasy), THC, phencyclidine, cotinine, alcohol, and opiates. Presence of any drugs will be considered a screen failure.

Urinalysis will only be assessed during the Screening Visit and will summarized for both the Safety and ITT Population. Urine assessments include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range a microscopic examination will be performed and results provided as a listing.

9.7. Baseline Primary and Secondary Efficacy Evaluations

The primary objective of this study is to evaluate the efficacy of Cannabidiol Oral Solution as adjunct therapy to vigabatrin in treating infantile spasms. Efficacy will be evaluated using the following primary and secondary endpoints.

Primary Efficacy Analysis

- Percent of patients with resolution of both infantile spasms and hypsarrhythmia or a pattern of epileptic encephalopathy at Day 14 (complete response) will be compared between Vigabatrin plus Placebo and Vigabatrin plus CBD 40 mg/kg/day groups.

Secondary Efficacy Analyses

- Percent of patients with resolution of infantile spasms at Day 14 will be compared between treatment groups.
- Percent of patients with resolution of hypsarrhythmia or a pattern of epileptic encephalopathy at Day 14 will be compared between treatment.
- Investigator impression of efficacy and tolerability of study drug (Clinical Global Impression – Global Improvement (CGI-I) will be compared between treatment groups.
- Percent reduction in spasm-free days between the Initial Treatment Period (Days 1 to 14) and Screening Period (Days -14 to -1) will be compared between treatment groups.
- Percent of patients who relapse during the Extended Treatment Period will be compared between 14-day Vigabatrin + CBD responders and 14-day Vigabatrin + placebo responders. Time to relapse will be calculated and compared.
- Percent of patients with partial response at Day 14 who achieve complete response during the Extended Treatment Period will be compared. Time to complete response will be calculated and compared.

Baseline Video-EEG results (Presence of spasms, number of spasms, and presence of hypsarrhythmia, presence of epileptic encephalopathy) will be summarized by treatment group for both Awake and Sleep periods.

Historical seizure history will be recorded during the Screening Visit based on parent/caregiver recollection. Baseline percent of spasm-free days will be calculated using the seizure diary collected during the Screening Period and summarized by treatment arm.

9.7.1. Imputation for Missing Data

No imputation of missing values is planned for this study. Missing or partially missing dates will be imputed as described in 6.4.4.

10. EFFICACY

10.1. General Considerations

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

10.2. Testing Statistical Assumptions Including Comparability at Baseline

The statistical assumptions of ANCOVA are:

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

These assumptions will be assessed using boxplots, Q-Q plots, and scatter plots with regression lines for each treatment group. If interaction between the independent variables is suspected, interaction terms will be tested in the regression model. The additional assumption of random independent samples is insured by the use of a randomized, double-blind experimental design.

Comparability at Baseline will be assessed by comparison of treatment groups for the Baseline values using ANCOVA or Fisher's Exact Test. Potentially important imbalances between treatment groups will be assessed for their impact on efficacy analysis by including them as covariates in a linear mixed model and possible supportive sub-group analyses, as appropriate.

Patients will be randomized to treatment group stratified by developmental status. Comparability of strata will be assessed by comparison of strata within treatment groups using ANCOVA and Fisher's exact test. If significant differences in the efficacy endpoints are found between strata, a stratified analysis will be performed. Otherwise, data from each strata will be pooled and presented as overall differences between treatment groups.

10.3. Statement of the Null and Alternate Hypotheses

10.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint in this study is:

- Percent of patients who are considered complete responders, defined as complete resolution of spasms and hypsarrhythmia or a pattern of epileptic encephalopathy

confirmed by 24-hour video-EEG from Day 13 to Day 14, as determined by the Independent Central Reader.

Null hypothesis: There is no difference in the percent of patients defined as complete responders between treatment groups.

Alternative hypothesis: Treatment groups have significantly different percent of complete responders.

10.3.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints:

- Percent of patients with absence of infantile spasms as assessed by 24-hour video-EEG from Day 13 to Day 14 (partial response).

  Null hypothesis: There is no difference in the percent of patients with absence of infantile spasms between treatment groups.

  Alternative hypothesis: Treatment groups have significantly different percentage of patients with absence of infantile spasms.

- Percent of patients with absence of hypsarrhythmia or pattern of epipleptic encephalopathy as assessed by 24-hour video-EEG from Day 13 to Day 14 (partial response).

  Null hypothesis: There is no difference in the percent of patients with hypsarrhythmia or pattern of epipleptic encephalopathy at Baseline but absence of hypsarrhythmia or pattern of epipleptic encephalopathy at Day 13 to Day 14 between treatment groups.

  Alternative hypothesis: Treatment groups have significantly different percent of patients with hypsarrhythmia at Baseline but absence of hypsarrhythmia at Day 14 to Day 15.

- Investigator impression of efficacy and tolerability of study drug (CGI-I) at End of Study/Early Withdrawal (Visit 5).

  Null hypothesis: There is no difference in the mean CGI-I score between treatment groups.

  Alternative hypothesis: Treatment groups have significantly different mean CGI-I score.

- Percent reduction in spasm-free days between the Initial Treatment Period (Days 1 to 14) and Screening Period (Days -14 to -1), as determined by the seizure diary entries.

  Null hypothesis: There is no difference in the percent reduction in spasm-free days between treatment groups.

  Alternative hypothesis: Treatment groups have significantly different percent reduction in spasm-free days.

- For patients with a complete response during the Initial Treatment Period who continue: percent of patients who relapse during the Extended Treatment Period confirmed by video-EEG following parent report of relapse, and time to relapse.

1. *Null hypothesis: there is no difference in the relapse rate between Vigabatrin + Placebo Responders and Vigabatrin + CBD Responders.*

   Alternative Hypothesis: The relapse rate is different Vigabatrin + Placebo Responders and Vigabatrin + CBD Responders.

2. *Null hypothesis: there is no difference in time to relapse between Vigabatrin + Placebo Responders and Vigabatrin + CBD Responders.*

   Alternative Hypothesis: The time to relapse is different Vigabatrin + Placebo Responders and Vigabatrin + CBD Responders.

- For patients with partial response during the Initial Treatment Period who continue: percent of patients who achieve complete response during the Extended Treatment Period, confirmed by video-EEG following parent report, and time to complete response.

  1. *Null hypothesis: there is no difference in the percentage of patients achieving complete response in the Extended Treatment Period between Vigabatrin + Placebo Partial Responders and Vigabatrin + CBD Partial Responders.*

     Alternative Hypothesis: The percentage of patients achieving complete response in the Extended Treatment Period is different Vigabatrin + Placebo Partial Responders and Vigabatrin + CBD Partial Responders.

  2. *Null hypothesis: there is no difference in time to complete response between Vigabatrin + Placebo Partial Responders and Vigabatrin + CBD Partial Responders.*

     Alternative Hypothesis: The time to complete response is different Vigabatrin + Placebo Partial Responders and Vigabatrin + CBD Partial Responders.

10.4. Subgroup Analyses

No subgroup analysis is planned. However, if significant differences in efficacy endpoints are observed between developmentally normal vs. delayed patients, stratified analysis will be performed.

10.5. Multiple Comparisons and Multiplicity

No multiple comparisons are planned for analysis of the Primary Efficacy Endpoint. Secondary Endpoints will have an FDR correction applied to control the overall q = 0.05.

10.6. Analysis of the Primary Efficacy Endpoints

The primary efficacy endpoint will be assessed on the ITT population.

10.6.1. Primary Efficacy Analysis

The primary efficacy endpoint in this study is:

- Percent of patients who are considered complete responders, defined as complete resolution of spasms and hypsarrhythmia or a pattern of epileptic encephalopathy.

The percent of complete responders will be calculated for each treatment group and compared using Fisher's exact test.

10.6.2. Presentation of the Primary Efficacy Results

Percent of patients considered complete responders in each treatment group will be reported in a table. The p-value for difference between groups will be presented.

10.7. Analysis of the Secondary Efficacy Endpoints

10.7.1. Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- Percent of patients with resolution of infantile spasms as assessed by 24-hour video-EEG from Day 13 to Day 14 (partial response).
- Percent of patients with resolution of hypsarrhythmia or pattern of epipleptic encephalopathy as assessed by 24-hour video-EEG from Day 13 to Day 14 (partial response).
- Investigator impression of efficacy and tolerability of study drug (CGI-I) at Visit 5 (End of Study) or Early Withdrawal.
- Percent reduction in spasm-free days between the Initial Treatment Period (Days 1 to 14) and Screening Period (Days -14 to -1), as determined by the seizure diary entries.
- For patients with a complete response during the Initial Treatment Period who continue: percent of patients who relapse during the Extended Treatment Period confirmed by video-EEG following parent report of relapse, and time to relapse.
- For patients with partial response during the Initial Treatment Period who continue: percent of patients who achieve complete response during the Extended Treatment Period, confirmed by video-EEG following parent report, and time to complete response.

Percentage of patients with partial response will be compared for each endpoint between treatment groups using Fisher's exact test.

Parent impression of efficacy and tolerability as measured by Clinical Global Impression – Global Improvement Scale (CGI-I) will be summarized by visit and status of response (complete/partial and no response). Appropriate summary statistics will be displayed and the CGI-I will also be analyzed as a continuous scale:

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

Percent reduction in spasm-free days, will be calculated for each treatment group. Treatment groups will be compared using ANCOVA with baseline number of spasm-free days as a covariate.

Percent of Responders who relapse and Partial Responders who achieve complete response during the Extended Treatment Period will be compared between treatment groups using Fisher's exact test. Time to relapse and time to complete response will be visualized using Kaplan-Meier curves and compared with log-rank tests.

10.7.2. Presentation of the Secondary Efficacy Results

Percentage of Partial Responders at Day 14 will be summarized by treatment group and developmental stage, and the p-value presented. CGI-I results will be summarized as a frequency table and the mean and median score with the p-value. Percent change in spasm-free days, relapse rate, and rate of partial to complete response will be summarized by treatment group and p-value. Time to relapse and time to complete response will be presented by treatment group as Kaplan-Meier curves and p-value for log-rank test.

10.8. Summary of Reasons for Efficacy Non-evaluability/Exclusion from Efficacy Analyses

If any patient is excluded from either the Safety or ITT Population, these will be presented in a listing with the reason for exclusion.

11. SAFETY AND TOLERABILITY

11.1. Overall Summary of Tolerability

The secondary objective of the study is to evaluate the safety and tolerability of Cannabidiol Oral Solution as adjunctive therapy with either vigabatrin or ACTH as initial therapy in treating patients with Infantile Spasms. This objective will be met by assessment of the following:

- Treatment-emergent AEs (TEAEs) and SAEs graded according to the Medical Dictionary for Regulatory Activities (MedDRA version 19.0 or above). These will be captured at every patient visit to the study center.
- Liver function tests.
- Complete blood counts.
- Concomitant medications
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate).
- Physical and neurological examinations.

Collection and monitoring of these data are detailed in Sections 6.2.1 through 6.2.5 of the protocol.

11.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

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

11.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

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, SAEs, and deaths, if any, will be provided.

11.2.2. Missing and Partial AE Onset Dates

Imputation of missing and partial dates is described in Section 6.4.4.

11.2.3. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

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

11.3. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

Exposure to study medication in days will be presented for the Safety Population, by treatment category and overall. Patients are expected to complete the study drug as prescribed, however, if safety or tolerability issues arise the patient will be counted as a treatment failure and discontinued. The following parameters will be summarized by assigned treatment group:

- Total duration of study medication at any dose
- Number and percent of patients who received their full randomized dose for the duration of the study
- Compliance with prescribed dosing (Number and percent of patients who had at least one dose modification, changed, interrupted, or permanently discontinued)

Interruptions, compliance, and dose changes are not included in the calculation of duration of exposure. Total duration of study medication is defined as the number of days between date of first study medication administration to date of last study medication administration + 1.

The corresponding listing will present first/last dose dates, does the subject complete the treatment duration, reason for end of treatment and duration of exposure (days).

In addition, dose modifications will be summarized by treatment and overall in terms of:

- Number of subjects with at least one dose modification (as defined Section 14.1)
- Number of subjects with at least one dose changed
- Number of subjects with at least one dose interrupted
- Number of subjects with dose permanently discontinued
- Number of subjects per reason of dose modification
    - 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.

11.4. Concomitant and Other Medications

Concomitant Medications will be summarized using WHO-DD version March 2017 preferred terms (PT). Any medication/therapy that stops at or after this time or with missing stop dates is considered concomitant medication/therapy. Listings and summaries will be presented separately for the Safety Population.

11.4.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

Imputation of missing and partial dates is described in Section 6.4.4.

11.5. Routine Laboratory Data

Clinical laboratory findings will be summarized for all subjects in the Safety Population for observed values and change from baseline by visit. Shifts from baseline according to normal range criteria will also be presented for all subjects in the Safety Population.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

For Hematology the following parameters will be summarized: *Platelet Count, White Blood Cell Count (WBC), Neutrophils (Percent), Neutrophils (Absolute), Lymphocytes (Percent), Lymphocytes (Absolute), Eosinophils (Percent), Eosinophils (Absolute), Basophils (Percent), Basophils (Absolute), Monocytes (Percent), Monocytes (Absolute), Hemoglobin* and *Hematocrit.*

For Serum Chemistry the following parameters will be summarized: *Total Protein, Albumin, Creatinine, Blood Urea Nitrogen, Uric Acid, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, Asparate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyl transferase (GGT), FSH, Glucose, Calcium, Chloride, Bicarbonate, Sodium, Potassium* and *Phosphorus.*

The clinical laboratory data for each visit will be listed and summarized.

11.6. Vital Signs

Vital signs will be summarized for all subjects in the Safety Analysis Population for observed values and change from baseline as appropriate by visit for the following parameters: *Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Respiratory Rate, and Temperature*.

Shifts from baseline according to normal and abnormal criteria will also be presented for all subjects the Safety Population.

11.6.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg

Variable	Unit	Low	High
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart rate	Bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Body temperature	˚C	NA	≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C

11.7. Physical Examination

Physical examination at Screening will be summarized as percent of patients with 'normal' vs. 'abnormal' findings for the following body systems: *General Appearance, Skin, Eyes, Ears, Nose, Throat, Neck, Lymph Nodes, Chest, Heart, Abdomen, Extremities, Neurological Systems, and Other*. Abnormal findings will be presented as a listing.

11.8. Neurological Examination

Neurological examination results at Screening will be summarized as percent of patients with 'normal' vs. 'abnormal' findings for *mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait,* and *station.*

Shifts from baseline according to normal and abnormal criteria will also be presented for all subjects the Safety Population for each visit. Abnormal findings will be presented as a listing.

11.9. PK Results

Trough values from the PK analysis obtained at Visit 5 will be presented as a listing and summarized by treatment arm and Response status (defined from the 24-hour video-EEG performed from Day 13 to Day 14).

11.10. Study Termination Status

Study completion/termination status will be listed for each patient, including reasons (if applicable) for early termination.

12. INTERIM ANALYSES

No interim analysis is planned.

13. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.

2. US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320.

3. Guidance for Industry (2014) Analgesic Indications: Developing Drug and Biological Products - Draft Guidance. Department of Health and Human Services: Food and Drug Administration. Center for Drug Evaluation and Research (CDER) February 2014 Clinical/Medical.

14. APPENDIX

14.1. Sample Table of Contents for Data Listings

Title		Population	Comments
Study Population Section			
9.1.1	Patient Enrollment and Randomization	All	Unique
9.1.2	Patient Disposition	All	Unique
9.1.3	Subjects who did not Satisfy Inclusion/Exclusion Criteria (if applicable)	Screening Failure	
	Protocol Deviations	Safety	Unique
10.1.1	Demographics and Baseline Characterics	Safety	
10.2.1	Medical/Surgical History	Safety	
10.3.1	Prior and Concomitant Medications	Safety	
10.3.2	Non-Medication Therapy	Safety	
10.6.1	Serology Laboratory and Pregnancy Test Results	Safety	
10.6.2	Urine Drug Screen	Safety	
12.3.1	Study Drug Administration	Safety	
12.3.2	Drug Accountability	Safety	
12.2.1	All Treatment Emergent Adverse Events (TEAEs)	Safety	
12.2.2	Treatment Related TEAEs	Safety	
12.2.3	Serious TEAEs	Safety	
12.2.4	Deaths	Safety	
12.2.5	TEAEs Leading to Premature Study Discontinuation	Saftey	
12.6.1	Chemistry Laboratory Results	Safety	
12.6.2	Hematology Laboratory Results	Safety	
12.6.3	Urinalysis Laboratory Results	Safety	
12.7.1	Vital Signs	Safety	
12.8.1	Physical Examinations	Safety	
12.9.1	Neurological Examinations	Safety	

14.2. Sample Table of Contents for Data Display Summaries

	Title	Population	Comments
Study Population Section			
9.1.1	Summary of Subject Disposition	Randomized	Unique
7.4.1	Summary of Analysis Populations	Randomized	Unique
10.1.1	Summary of Demographic Characteristics	Safety	Unique
10.1.2	Summary of Demographic Characteristics	ITT	Repeat 9.3.1
Efficacy Section			
Figures			
11.7.1	Correlation between trough plasma drug levels and response	ITT	Unique
11.6.2		ITT	Unique
Tables			
11.6.1	Summary of Complete Responders	ITT	Unique
11.7.1	Summary of Partial Response – absence of spasms	ITT	Unique
11.7.2	Summary of Partial Response – absence of hypsarrhythmia	ITT	
11.7.3	Summary of Investigator CGI-I at End of Study/Early Withdrawal	ITT	Unique
13.1	Median Reduction in Seizure Burden and Percent of Spasm-Free Days	ITT	Unique
		ITT	Unique
Safety Section			
12.3.1	Summary of Exposure to Dronabinol Oral Solution by Treatment Group	Safety	Unique
12.2.1	Summary of Adverse Events by Treatment Group	Safety	Unique
12.2.2	Summary of Death and Serious Adverse Events by Treatment Group	Safety	Unique
12.2.4	Summary of Drug-Related Adverse Events by Treatment Group	Safety	Unique
12.6.1	Listing of Subjects Who Became Pregnant During the Study	Safety	Unique
12.6.2	Summary of Actual Values and Changes from Baseline in Clinical Chemistry Data by Treatment Group and Study Time	Safety	Unique
12.6.3	Summary of Actual Values and Changes from Baseline in Hematology Data by Study Time	Safety	Unique
12.7.1	Summary of Actual Values and Changes from Baseline in Vital Signs by Treatment Group and Study Time	Safety	Unique
12.8.1	Summary of Physical Examination Results		
12.9.1	Summary of ECG Data	Safety	Unique