NCT#: NCT03421496

CLINICAL TRIAL PROTOCOL

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 Patients with Infantile Spasms

Protocol Number:	INS011-16-082
Final Protocol Date:	12 Jan 2018
Amendment 1 Date:	22 Feb 2018
Amendment 2 Date:	05 Jul 2018
Protocol Version:	5.0
Investigational Product:	Cannabidiol Oral Solution
IND Number:	123120
EudraCT Number:	2018-001523-40
Sponsor:	Insys Development Company, Inc. 1333 South Spectrum Blvd, Suite 100 Chandler, AZ 85286
Medical Monitor:	[redacted] Insys Development Company, Inc. [redacted] Phone: [redacted] Fax: [redacted]

Confidentiality Statement

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements. The confidential information in this document is provided to you as an investigator, potential investigator or consultant for review by you, your staff and applicable Independent Ethics Committee (IEC) or Institutional Review Board (IRB). It is understood that the information will not be disclosed to others without written authorization from Insys Development Company, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

PROTOCOL APPROVAL PAGE

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 Patients with Infantile Spasms

Protocol Approved by:

[redacted]

Insys Development Company, Inc. Date: [redacted]

[redacted]

Insys Development Company, Inc. Date: [redacted]

[redacted]

Insys Development Company, Inc. Date: 10 July 2018

PROTOCOL SYNOPSIS

Name of Sponsor/Company:

Insys Development Company, Inc.

Name of Investigational Product:

Cannabidiol Oral Solution

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 Patients with Infantile Spasms

Study center(s): Approximately 40 sites in the US and ex-US.

Phase of development: Phase 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 Cannabidiol Oral Solution after the 14-day treatment with vigabatrin or vigabatrin plus Cannabidiol Oral Solution is complete.
- 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 occur during Visit 2 to one of two treatment groups:

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

Approximately 190 patients in total will be enrolled into one of the two treatment arms; 130 patients in the investigational product arm with 60 patients in the placebo arm. Patients will be dosed approximately every 12 hours with meals to help ensure consistent plasma levels are achieved and to reduce variability.

Doses of CBD exceeding 40 mg/kg/day will not be examined in this study. 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 1 to 24 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 140 days.

Screening Period:

Each newly diagnosed patient with Infantile Spasms will complete a Screening Period and will have up to 14 days to enroll in the study.

Patients will have a 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 and a 24-hour video-EEG at Visit 5 (Day 14) of the Initial Treatment Period to establish their final level of infantile spasms and hypsarrythmia. A blinded central reader, not involved in the study, will evaluate the video-EEGs and determine responder status. Details of the video-EEG assessment will be provided in the video-EEG Charter. The treatment response categories are summarized in Table 1 below. In addition, a 9-hour video EEG will be conducted during the Extended Treatment Period to confirm parent/caregiver reports of relapse. If possible, a 9-hour video EEG will be conducted for patients who have continued into the Extended Treatment Period and decided to Early Withdraw. A video EEG is not required for patients who decide to withdraw during the Initial Treatment Period.

Table 1: Video EEG Response Definitions

Response Category	Definition
Complete Response	Complete resolution of spasms and hypsarrythmia confirmed by video EEG
Partial Response	Complete resolution of either spasms or hypsarrythmia confirmed by video EEG
Non-Response	No improvement or worsening of spasms/hypsarrythmia burden

Initial Treatment Period

- Day 1 (Visit 2): Patients will receive the initial 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 BID for 3 days.
- 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,

concomitant medications, height/weight, and assess adverse events (AEs). For those patients who tolerate the initial dose, the dose for vigabatrin will be increased to 100 mg/kg/day (BID), and either CBD 30 mg/kg/day and matching CBD 10 mg/kg/day placebo, or CBD 40 mg/kg/day placebo BID for 3 days.

- Day 7 (Visit 4): Patients will return to the study center to evaluate medical status (seizure diary, vital signs, and neurological exam), clinical laboratory assessments, concomitant medications, height/weight, and assess AEs. For those patients who tolerate the increased doses, the dose of vigabatrin will be increased to 150 mg/kg/day and CBD or CBD placebo to 40 mg/kg/day BID for the remaining 9 days. Vigabatrin, CBD, and matching placebo will be administered in a twice daily fashion at 12-hour intervals with meals.
- As part of their standard of care, investigators will assess safety and tolerability of the treatment regimens throughout the study period. All subjects will continue treatment until confirmation from the central reader on the 24-hour video EEG and clinical laboratory results are received.

Extended Treatment Period

Following the Initial Treatment Period:

- Complete Responders will continue receiving their assigned treatments of vigabatrin plus either CBD 40 mg/kg/day or matching placebo for 75 days, until Week 13 (Day 90) to monitor treatment response.
- During the Extended Treatment Period, the investigator may reduce the dose of CBD or CBD placebo to 30 mg/kg/day for safety or tolerability. If the subjects cannot tolerate the 30 mg/kg/day, they will be discontinued from the study following the completion of the taper period.

Partial Responders:

Partial responders will be offered the opportunity to enroll in an open-label safety study that allows investigators to combine standard-of-care treatment with CBD.

Taper Period

Following the completion of the Initial Treatment Period (Visit 6), partial responders who do not enroll in the open-label safety study and non-responders will have vigabatrin and CBD or CBD placebo tapered as follows:

- Vigabatrin taper: 150 mg/kg/day will be reduced to 100 mg/kg/day for 3 days, then the 100 mg/kg/day dose will be reduced to 50 mg/kg/day for 3 days, and then discontinued.
- CBD or CBD Placebo taper: 40 mg/kg/day will be reduced to 30 mg/kg/day for three days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for 3 days, and then discontinued.

Complete Responders will be tapered off vigabatrin and CBD at the completion of the Extended Treatment Period, and all patients will be tapered off at any Early Withdrawal Visits, using the same schedules as described above.

If the investigator decides to continue vigabatrin as a treatment for patients at the end of the study or early withdrawal, tapering of vigabatrin will be left to the discretion of the PI.

CBD requires tapering off at the End of Study or at the Early Withdrawal visit.

Follow-up Period

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

Study Assessments

To assess efficacy, a 24-hour video-EEG, daily seizure diaries, meal diary 24 hours prior to and through PK blood sampling 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 Day 14 (Visit 5) through Day 15 (Visit 6). The EEGs and hypsarrythmia will be evaluated by a blinded central reader who is not involved with the study. Further details will be provided in the video-EEG Charter.
- Daily seizure diaries will be completed throughout the Initial and Extended Treatment Periods.
- The CGI-I will be completed by the investigator at Visit 6 of the Initial Treatment Period, or at Early Withdrawal. The CGI-S will be completed by the investigator at Screening.

Safety assessments for all patients will include medical history, physical and neurological examinations, vital signs (seated or supine blood pressure [depending on patient age and ability], pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, liver enzymes, and serum bilirubin), prior medication history (assessment of past/current AETs and concomitant medications), and AE assessments will be conducted at specific visits throughout the study. In addition to the safety assessments required by the study protocol, the investigator will monitor patients as recommended in the current FDA-approved vigabatrin prescribing information.

A blood sample for PK analysis of CBD and the metabolite 7-hydoxy-CBD (7-OH-CBD) will be obtained on Day 15 prior to the second dose during the 24-hour video-EEG. A meal diary will be used to record the type of meals consumed in relation to PK blood draws.

If a patient discontinues the study prematurely, the investigator'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 190 patients (130 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 1 and 24 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.

Inclusion criteria

A patient will be eligible for study participation if the patient meets all of the following criteria:

1. Parent(s)/caregiver(s) fully comprehends and signs the informed consent form, understands 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 1 month to 24 months of age (inclusive) at time of consent.
3. Clinical diagnosis of Infantile Spasms, confirmed by video-EEG (including at least one cluster of electroclinical spasms [≥3 in any 10-minute epoch] and hypsarrythmia) obtained during the Screening Period and read by a central reader.
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.

Exclusion criteria

A patient must not meet any of the following criteria:

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 drug.
2. Known or suspected allergy to cannabidiol.
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 suspected 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. Patient currently on any disallowed CYP3A4-related medication listed in Appendix 1 (phenytoin, fluvoxamine, carbamazepine, and St. John's Wort).
9. Previously received any investigational drug or device or investigational therapy within 30 days before Screening.
10. 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). The investigator may deem the patient eligible if he or she judges the laboratory values to be not clinically significant.

Investigational product, dosage, and mode of administration:

Cannabidiol Oral Solution, manufactured for and supplied by Insys Manufacturing LLC. During the Initial Treatment Period: 20, 30, and 40 mg/kg CBD BID. During the Extended Treatment Period: 40 mg/kg CBD BID (or 30 mg/kg if dose is reduced) for Complete Responders.

Duration of treatment:

The maximum duration of the study from screening to follow-up of AEs will be approximately 140 days.

Reference therapy, 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 3 days, then 150 mg/kg/day for 9 days.

Criteria for evaluation:

Efficacy

Primary efficacy endpoint

- Percent of patients who are considered complete responders, defined as complete resolution of spasms and hypsarrhythmia confirmed by 24-hour video EEG from Day 14 to Day 15, 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 14 to Day 15 (partial response).
- Percent of patients with resolution of hypsarrhythmia as assessed by 24-hour video EEG from Day 14 to Day 15 (partial response).
- Investigator impression of efficacy and tolerability of study drug (CGI-I) at Visit 6 (End of Study) or Early Withdrawal.
- Increase in the number of spasm-free days between Day 1 and Day 15 of the Initial Treatment Period, 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.

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, liver enzymes and serum bilirubin.

Pharmacokinetics

Trough concentrations (C_{trough}) of cannabidiol (CBD) and 7-OH-CBD will be used to assess the exposure-response relationship. A meal diary will be used to record the type of meals consumed in relation to the PK blood draws.

Statistical methods:

Sample Size Calculation

A total of 190 patients (130 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 60%.

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.
- PK Population: The PK Population will include all patients who were treated with at least one dose of the study drug and have at least one usable PK measurement.

Efficacy Analyses

The ITT Population will be used for all efficacy analyses in the Initial Treatment Period.

- 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, a fixed sequence multiple comparisons correction with fallback will be used. The assignment of alpha levels to hypotheses being tested will be specified in the Statistical Analysis Plan.
- 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 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 a chi-square test will be used for inferential statistics.

<u>Primary Efficacy Analysis</u>

- Percent of patients with complete resolution of both infantile spasms and hypsarrhythmia at Day 15 (complete response) will be compared between vigabatrin plus placebo and vigabatrin plus CBD 40 mg/kg/day groups using a chi-square test.

<u>Secondary Efficacy Analyses</u>

- Percent of patients who relapse during the Extended Treatment Period will be compared between 14-day complete responders receiving vigabatrin + CBD and complete responders receiving 14-day vigabatrin + placebo using chi-square test. Time to relapse will be described with Kaplan-Meier curves and treatment groups compared using a log-rank test.

- Percent of patients with complete resolution of infantile spasms at Day 15 will be compared between treatment groups using a chi-square test.
- Percent of patients with complete resolution of hypsarrhythmia at Day 15 will be compared between treatment groups using a chi-square test.
- Investigator impression of efficacy and tolerability of study drug (Clinical Global Impression – Global Improvement [CGI-I]) will be compared between treatment groups using ANCOVA with baseline CGI-S as a covariate.
- Reduction in percentage of spasm-free days between the Initial Treatment Period and Screening Period will be compared between treatment groups using ANCOVA with the Screening Period percent spasm-free days as a covariate.

Secondary Efficacy Analyses for patients with a complete response during the Initial Treatment Period who continue to the Extended Treatment Period:

- Percent of patients who relapse during the Extended Treatment Period confirmed by video-EEG following parent report of relapse.
- Time to relapse.

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. Patients without a video EEG assessment on Days 14-15 will be considered non-responders for all EEG-related endpoints. Percentage of spasm-free days will be calculated based on the number of entries (up to 15 days per measurement period). 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.

Table 1: Schedule of Events

	SCREENING PERIOD	INITIAL TREATMENT PERIOD					EXTENDED TREATMENT PERIOD				Taper Period	Follow-up Period
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Day	**-14 to -1**	**Titration Days 1**	**Titration Day 4**	**Day 7**	**Day 14[a]**	**Day 15 EOS[b] (+ 5 days)**	**Week 6**	**Week 10**	**Week 13 EOS[b]**	**Early Withdrawal[m]**	**6 days**	**30 days**
Signed ICF	X											
Video-EEG	X[c]				X[c] → X[c]		----------X[c] ----------			X[c]		
Review of inclusion/exclusion criteria	X											
Demographics	X											
Assessment of current AETs	X					X	X	X	X	X	X	X
Medical/surgical history	X											
Seizure History[d]	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X		
Clinical Labs	X		X	X		X	X	X	X	X		
Physical Exam	X											
Height/Weight	X		X	X	X	X	X	X	X	X		
Head Circumference	X					X			X	X		

	SCREENING PERIOD	INITIAL TREATMENT PERIOD					EXTENDED TREATMENT PERIOD				Taper Period	Follow-up Period
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**			
Day	**-14 to -1**	**Titration Days 1**	**Titration Day 4**	**Day 7**	**Day 14[a]**	**Day 15 EOS[b] (+ 5 days)**	**Week 6**	**Week 10**	**Week 13 EOS[b]**	**Early Withdrawal[m]**	**6 days**	**30 days**
Neurological Exam[f]	X	X	X	X	X	X	X	X	X	X		
Study Drug Dosing		X[g]	X[h]	X[h]	X[h]	X[i]	X[i]	X[i]	X[i]	X[i]	X[j]	
Assess AEs		X	X	X	X	X	X	X	X	X	X	X
PK blood sampling[k]						X						
Investigator CGI-S	X											
Investigator CGI-I						X				X		
Seizure Diary[l]	X	X	X	X	X	X	X	X	X	X	X	
Meal Diary[n]					X	X						

Abbreviations: AE = adverse event; AETs = antiepileptic therapies; CGI-I = Clinical Global Impression-Global Improvement Scale; CGI-S = Clinical Global Impression-Severity; EEG = electroencephalography; EOS = End of Study; ICF = informed consent form; PK = pharmacokinetic.

[a] Patients will be admitted to the study center as an inpatient on Day 14 and discharged on Day 15 following the completion of End of Study assessments.

[b] End of Study assessments will be completed at Day 15 for partial and non-responder patients and Week 13 for patients who complete the extension period of the study.

[c] Patients will have a minimum of a 9-hour video EEG that includes at least one full sleep-wake cycle during their Screening Visit and a 24-hour video EEG at Visit 5 (Day 14 to Day 15) during the Initial Treatment Period. A minimum of 9-hour video-EEG will be performed during the Extended Treatment Period to

confirm parent/caregiver report of relapse or complete resolution or at Early Withdrawal for patients who have continued into the Extended Treatment Period. A Video EEG is not required for patients who decide to withdraw during the Initial Treatment Period

[d] To assess preliminary efficacy, a seizure history will be collected at screening to record the approximate number of seizures in the last 28 days as reported by the parent/caregiver.

[e] Vital signs will be taken after approximately 5 minutes seated or supine, depending on patient ability. On Day 1(Visit 2), vital signs should be taken predose and at 4 hours postdose. On all other days, the assessment will be completed predose.

[f] A brief neurological examination will be performed, except for the Screening Visit, Visit 6, Visit 9 and Early Withdrawal which will be a complete neurological exam. On Day 4 (Visit 3), and Day 7 (Visit 4) a brief neurological examination will be performed predose and approximately 2 hours following administration of the morning dose of the investigational product. Additional examinations may be performed at the discretion of the investigator.

[g] On Day 1 (Visit 2), patients will receive the initial 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.

[h] For those patients who tolerate the initial dose, the dose for vigabatrin will be increased to 100 mg/kg/day [BID], and either CBD 30 mg/kg/day plus matching CBD 10 mg/kg/day, or CBD 40 mg/kg/day placebo for 3 days. On Day 7 (Visit 4) the dose of vigabatrin will be increased to 150 mg/kg/day and CBD to 40 mg/kg/day for the remaining 9 days for subjects who tolerate the previous dose.

[i] Complete Responders will continue receiving their assigned treatments of vigabatrin plus either CBD 40 mg/kg/day or matching placebo for 75 days, until Week 13 (Day 90) to monitor treatment response. During the extended treatment period the Investigator can only down titrate once to 30 mg/kg/day.

[j] All subjects will be tapered off vigabatrin as follows: 150 mg/kg/day will be reduced to 100 mg/kg/day for 3 days then the 100 mg/kg/day will be reduced to 50 mg/kg/day for 3 days and then discontinued. Similarly, all subjects will be tapered off CBD or CBD Placebo according to the following schedule: 40 mg/kg/day will be reduced to 30 mg/kg/day for 3 days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for 3 days, then discontinued. Patients will receive a follow-up phone call 4 weeks after completing the tapering. Drug reconciliation will be completed at the end of study.

[k] A blood sample for PK analysis will be obtained on Day 15 prior to the second dose during the 24-hour video EEG.

[l] A seizure diary will record daily spasms between Visit 1 and Visit 2. The daily spasm record will continue through the Initial Treatment and Extended Treatment Periods, and throughout the Taper period for patients enrolled in the Extended Treatment Period.

[m] Patients who discontinue the study drug early should return for the Early Withdrawal Visit.

[n] Meal diary must be collected 24 hours prior to and through PK blood sampling on Day 15 (Visit 6).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
5-HT_{1a}	5-hydroxytryptamine 1a
ACTH	adrenocorticotropic hormone
AE	adverse event
AET	anti-epileptic therapy
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
$AUC_{(0\text{-tau})}$	area under the plasma concentration-time curve to the end of the dosing period
BUN	blood urea nitrogen
CB1	cannabinoid receptor 1
CB2	cannabinoid receptor 2
CBD	Cannabidiol
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Global Improvement
CGI-S	Clinical Global Impression – Severity of Illness
cGMP	current Good Manufacturing Practices
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CV%	coefficient of variation
CYP	cytochrome P450
CYP1A1	Cytochrome P450 1A1
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19
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
ED_{50}	median effective dose
EEG	electroencephalogram
EENT	eyes, ears, nose, and throat
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	informed consent form
ICD	informed consent document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IS	Infantile Spasms
ITT	Intent to Treat
IV	Intravenous
LDH	lactate dehydrogenase
LFTs	liver function tests
MCT	Medium Chain Triglycerides
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No Observed Adverse Effect Level
OH	Hydroxy
PK	pharmacokinetic(s)
pKa	acid dissociation constant
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
$t_{½}$	terminal phase half-life
TD_{50}	median tolerated dose
TBL	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TLFs	tables, listings, and figures
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States

1. INTRODUCTION

Data presented in Section 1.0 include overviews from the nonclinical and clinical published literature that reports on various other formulations of cannabidiol (CBD) (primarily plant-based). Analogous studies have not been completed for Cannabidiol Oral Solution, the pharmaceutical grade synthetic CBD to be investigated in this study.

Please see the Investigator's Brochure (IB)[1] for more information.

1.1. Cannabidiol

The main active constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC) is the principal psychoactive constituent of marijuana. Cannabidiol is the second most abundant cannabinoid and highly physiologically relevant, but is non-psychoactive. It has demonstrated a potential benefit in treating patients with treatment-resistant epilepsy.[2,3,4,5]

Insys Development Company, Inc. (hereafter referred to as the Sponsor) has successfully manufactured a pharmaceutical grade, synthetic CBD drug substance. It is manufactured in their current Good Manufacturing Practices (cGMP) manufacturing facility. This facility is approved by the Drug Enforcement Administration (DEA) and has been inspected by the Food and Drug Administration (FDA). This active pharmaceutical ingredient is ≥99.5% pure[6] and can be consistently produced without the concern for contaminant.

1.1.1. Mechanism of Action

The mode of action of CBD is not fully understood. The drug substance manifests a low affinity for endogenous cannabinoid receptors 1 (CB1) and 2 (CB2). Cannabidiol acts as an indirect antagonist of CB1 and inhibits several CB1 mediated Δ^9-THC effects.[7] It also stimulates the vanilloid receptor type 1[8] and modulates the μ- and δ-opioid receptors.[9] It may also increase plasma Δ^9-THC levels by inhibiting its hepatic microsomal metabolism by competitively binding proteins in the cytochrome P450 (CYP) oxidative system.[10] Finally, CBD may modulate neuronal hyperexcitability through one or more of the following mechanisms:

- Bidirectional regulation of calcium homeostasis via the mitochondrial sodium/calcium exchanger.[11]
- Agonistic properties at 5-hydroxytryptamine 1a (5-HT_{1a}) receptors.[12]
- Enhancing endogenous adenosine levels in the central nervous system (CNS) by reducing adenosine re-uptake.[13,14]

Recent studies have shown that CBD dose-dependently increased seizure threshold in wild-type mice, an effect that was markedly reduced in transient receptor potential vanilloid 1 (TRPV1) channel knockout mice[15], and blocked the G protein-coupled receptor-55 (GPR-55) mediated increase of miniature excitatory postsynaptic currents (mEPSCs) frequency in CA1 pyramidal neurons in healthy and epileptic tissues.[16]

1.1.2. Metabolism and Potential Drug Interactions

The major biotransformation pathway for CBD is similar to that of other cannabinoids and mediated by hydroxylation by cytochrome P450 (CYP) proteins.[17] Its interactions with human drug metabolizing enzymes (as a substrate, inhibitor, or inducer) were recently reviewed.[18,19]

Cannabidiol is metabolized primarily in the liver by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 2C19 (CYP2C19). The effect of cannabidiol on primary fetal rat hepatocyte viability was investigated.[20] In vitro, hepatocytes showed reduced cell viability, inhibited cell growth, and cytoplasmic alterations after 24 hours of exposure to cannabidiol at concentrations of 10^{-4} to 10^{-3} M. Markers of cell injury increased following treatment of cannabidiol at concentrations of 10^{-4} M (160% of control after 24 hours of exposure) and 5×10^{-5} M (220% of control after 72 hours). These results correspond to other studies showing that cannabidiol is a potent inhibitor of hepatic drug metabolism.[21,22,23] Specifically, cannabidiol inhibits CYP3A4, cytochrome P450 3A5 (CYP3A5), and cytochrome P450 1A1 (CYP1A1) in vitro.[24,25,26] It also appears to inhibit cytochrome P450 2C9 (CYP2C9)[27] and the transport protein p-glycoprotein.[28,29]

Cannabidiol likely inhibits drug metabolism when one of its metabolites binds to hepatic microsomal CYP proteins.[30,31,32,33] Hexobarbital is metabolized by CYP2C9 and the duration of sleep induced by hexobarbital may be used as a surrogate for drug metabolism. Using this outcome measure, it was shown that suppression of drug metabolism by cannabidiol diminished following repeated exposure to the drug substance in rodents.[34]

Clinically, oral intake of cannabidiol (100 mg every 4 hours for 5 to 12 days) produced a 36% lower clearance and 35% lower volume of distribution of hexobarbital in healthy volunteers.[35] Notably, this study also showed that liver function tests (LFTs) remained normal before and during cannabidiol ingestion. Cannabidiol also inhibited barbiturate metabolism in humans to an extent substantially greater than that observed for Δ^9-THC. Conversely, another study reported that oral dosing with cannabidiol (25 mg/kg) did not significantly affect the total clearance, volume of distribution, or terminal elimination $t_{1/2}$ of Δ^9-THC metabolites.[36]

1.2. Nonclinical Experience

1.2.1. Safety

Nonclinical toxicological assessments of CBD conducted by Insys Development Company, Inc. thus far have concluded that 600 mg/kg/day exceeded the maximum tolerated dose in adult rats. Female rats generally appear to be more sensitive to the effects of CBD (in terms of toxicity) than similarly treated males. Because of the microscopic findings in the skin (follicular atrophy) noted in both genders at all CBD dose levels, a No Observed (Adverse) Effect Level (NOAEL) could not be determined for this study. The main GLP 6-month adult rat and 9-month cynomolgus monkey chronic toxicity studies with CBD in Medium Chain Triglycerides (MCT) are underway with few clinical signs being observed in either study.

Observations from single- and repeat-dose toxicology studies in rats and non-human primates demonstrate that CBD-induced hypoactivity is transient and does not induce psychopharmacological effects[37]. In rats, inhalation exposure of up to 1.6 mg/kg/day of CBD (smoke) once daily for 14 days was associated with a transient dose-related hypoactivity (and prostration) and body weight gain was depressed[38]. The target organ for toxicity was the testes (impairment of spermatogenesis and sperm maturation).

In monkeys, a single intravenous dose of CBD produced dose-related hypoactivity, sedation, and prostration.[36] Tremors and convulsions occurred at >150 mg/kg and mortality at ≥225 mg/kg (associated with respiratory arrest and cardiac failure). Liver weights were increased and testes

`weights were decreased in the 200 mg/kg groups. Whether these effects on liver and testes were test-article related could not be conclusively determined due to the small sample size. There were no other meaningful treatment-related changes in clinical signs, body weight, core body temperature, or clinical or gross anatomic pathology.

In a 90-day repeated-dose oral toxicity study in monkeys, CBD (30 to 300 mg/kg/day) did not result in mortality, clinical signs, or adversely affect physiological parameters, body weights or gains, food consumption, or ophthalmologic or electrocardiogram (ECG) evaluations.[39] Lower heart rates were observed in treated males only during the first month. The only target organ identified was the testes. Similar to the observations in rats, lower testes weights were associated with dose-related inhibition of spermatogenesis, which did not appear to be reversible within the 30-day recovery period. The NOAEL in the monkey was determined to be <30 mg/kg/day (<360 mg/m^2/day based on body surface area).

In rat fertility studies, CBD appears to affect testicular development[38,40], and reduce fertility (reproductive capacity) of males but not females.[41] There were no studies that assessed the potential for effects on embryofetal development. The effects of CBD on perinatal and postnatal development principally showed effects in the testes of developing male pups.

It is unclear whether the observed testicular effects on spermatogenesis are reversible or not, as recovery periods have not been of sufficient duration to allow recovery of the seminiferous epithelium.

1.2.2. Efficacy in Animal Models of Epilepsy

Plant-derived cannabidiol shows antiepileptic,[42] antipsychotic, anti-dystonic, anti-emetic, and anti-inflammatory properties in animal models.[43] These models support exploring the use of cannabidiol for the treatment of epilepsy.

As an example, the anticonvulsant activity of oral cannabidiol was investigated in adult rat model of seizures (induced by maximal electroshock or audiogenic sources).[44] Cannabidiol was effective against maximal electroshock-induced seizures (median effective dose [ED_{50}] = 18 mg/kg), but only minimally effective against audiogenic-induced seizures (ED_{50} ≥75 mg/kg). The neurotoxicity median tolerated dose (TD_{50}) was >100 mg/kg. Cannabidiol co-administered with different anti-seizure drugs (e.g., phenytoin or carbamazepine) increased or reduced their anticonvulsant activity, indicating that synergism or antagonism with cannabidiol was drug specific.

1.3. Clinical Experience

Clinical data described in the following sections were collected following administration of various extracts of cannabidiol as oral solutions or solid formulations. Early reports have indicated the cannabinoids, in particular CBD, may be efficacious in treating refractory epilepsy.[45, 46, 47, 48] In separate Phase 3 studies with a plant-derived purified CBD (Epidiolex®, GW Pharmaceuticals), patients with Dravet Syndrome and Lennox-Gastaut Syndrome (LGS) treated with 20 mg/kg/day demonstrated a significant decrease in the median monthly seizure rate when compared to controls.

1.3.1. Pharmacokinetics

In human subjects, the pharmacokinetics (PK) of tetrahydrocannabinol (THC) containing cannabinoids varies as a function of its route of administration.

Pulmonary assimilation of inhaled cannabinoids provides a maximum plasma concentration (C_{max}) within minutes.

The PK parameters of cannabidiol were evaluated in a group of five cannabis smokers.[42] A high plasma clearance (960 to 1560 mL/minute) was calculated. A terminal half-life ($t_{½}$) was not reached at 72 hours, but the available data indicated $t_{½}$ for cannabidiol of 27 to 35 hours (mean of 31 hours) after smoking.[21] The distribution volume was estimated to be approximately 30 L/kg. The mean $t_{½}$ for cannabidiol is 24 or 31 hours, respectively, when administered intravenously (IV) or inhaled.[49]

After oral administration of 0.6 mg/kg of cannabidiol in normal subjects, the plasma time concentration curves over 6 hours post dosing were similar to that after 0.3 mg/kg of THC.[50] Oral doses of cannabidiol (10 mg/kg/day) once daily for 6 weeks in patients with Huntington's disease resulted in mean weekly plasma concentrations of 5.9 to 11.2 µg/L.[51] The volume of distribution of cannabidiol was about 30 L/kg greater than for THC, and the plasma clearance was similar to that of THC, ranging from 58 to 94 L/hour (960 to 1560 mL/min). After an IV dose of 20 mg, the average $t_{1/2}$ for cannabidiol was 24 hours (range of 18 to 33 hours).[21,52] Following oral ingestion, psychotropic effects of THC set in with a delay of 30 to 90 minutes, reach their maximum after 2 to 3 hours, depending on the dose and specific effect.

Following doses of 10 mg cannabidiol in combination with 10.8 mg THC in an oral spray for 9 consecutive days, mean peak plasma concentrations were 1.14 (0.86) ng/mL for cannabidiol and 2.72 (1.47) ng/mL for THC. The median time to C_{max} (t_{max}) was 1.27 (range of 0.75 to 2.52) hours for cannabidiol and 1.50 (0.75 to 2.50) hours for THC.[53]

A Phase 1 clinical study examined the results of sublingual administration of 10 mg THC with that of 10 mg THC and 10 mg cannabidiol in cannabis-based medicinal extracts.[54] Despite administration of equivalent amounts of THC and cannabidiol, lower plasma concentrations of cannabidiol were consistently observed. Mean C_{max} concentrations for THC, cannabidiol, and 11-hydroxy (OH)-THC were 4.9, 3.3, and 4.5 ng/mL when 10 mg THC and 10 mg cannabidiol were administered. The t_{max} was approximately 4 hours for all three analytes.

The systemic availability of cannabidiol administered via the smoking route averages approximately 31% with inter-patient variability ranging from 11% to 45%.[21] The bioavailability of cannabidiol following oral administration is approximately 6%.[46]

1.3.2. Overview of Safety

Clinical studies in various human populations indicate that CBD has a favorable side-effect profile. Doses as high as 1500 mg are well tolerated.[55] No significant reactions or serious adverse events (SAEs) have been reported across a wide range of dosages in both acute and chronic settings. Bergamaschi et al.[19] recently reviewed the safety of CBD in humans examined in 221 patients across 21 studies. As detailed in the IB[1], no significant safety issues were reported.

Regarding doses of CBD that have been examined in other studies, daily doses of 200 to 300 mg CBD (or potentially more) may be safe.[2,56] Clinical evaluation and therapeutic ranges of CBD

doses have been reported to be between 10 and 1500 mg/day, with the majority of reports evaluating doses in the 300 to 600 mg/day CBD range. Further, between 300 and 1500 mg have been used in humans without toxicity or SAEs.[45,57,58,59]

1.3.3. Selected Clinical Safety Data

Insys study INS011-14-029 enrolled 62 patients with refractory seizures between 1 and 17 years of age. Cannabidiol Oral Solution, 300 mg/mL at doses between 10 mg/kg/day and 40 mg/kg/day were generally well tolerated and no patient discontinued. Fifty-two of the 61 patients enrolled into a long-term safety study (INS011-14-030). Study INS011-14-030 was a long-term, open-label, 48-week study for pediatric patients aged 1 year to 17 years with refractory epilepsy who participated in the Phase 1/2 Study INS011-14-029.

Insys recently completed a long-term safety study (INS011-14-030) in pediatric patients with refractory epilepsy who participated in the Phase 1/2 PK study (INS011-14-029). This study was a long-term, open-label, 48-week study for pediatric subjects aged 1 year to 17 years with refractory epilepsy who participated in the Phase 1/2 Study INS011-14-029. A total of 52 subjects (9 infants, 26 children, and 17 adolescents) were enrolled and received at least one dose of the investigational product in this study. Forty-five (86.5%) subjects completed the study including follow-up. Seven (13.5%) subjects prematurely discontinued treatment and study participation: 2 (3.8%) subjects due to AEs, 3 (5.8%) subjects due to withdrawal of consent, 1 (1.9%) subject due to death considered not related to investigational product, and 1 (1.9%) subject due to other reason (reported lack of efficacy).

The mean modal dose (defined as the dose with the longest duration) was 24.42 mg/kg/day and the mean total duration of study drug was 311.1 days. Overall, 13 subjects (14.4%) had dose reductions during the study: 12 subjects (13.3%) had dose reductions due to an AE and 1 subject (1.1%) had a dose reduction due to “other” reason. The incidence of dose reductions resulting from an AE was higher for subjects who received 40 mg/kg/day (8 subjects, 30.8%) compared with subjects who received 20-<30 mg/kg/day (6 subjects, 8.8%) and 30-<40 mg/kg/day (1 subject, 6.6%). No subjects who received 10-<20 mg/kg/day and no infants had dose reductions. The trend was to increase the doses over the course of the study. There were 39 subjects (43.3%) who had dose increases during the study. The incidence of dose increases was higher for subjects who received 10-<20 mg/kg/day (14 subjects, 100%) compared with subjects who received 20-<30 mg/kg/day (16 subjects, 47.1%) and 30-<40 mg/kg/day (9 subjects, 56.3%).

Overall, 47 subjects (90.4%) experienced ≥1 adverse event (AE) during the study. The following AEs were reported in at least five subjects during the study: seizure (16 subjects, 30.8%), upper respiratory tract infection (eight subjects, 15.4%), anemia (seven subjects, 13.5%), diarrhea (seven subjects, 13.5%), pyrexia (seven subjects, 13.5%), somnolence (seven subjects, 13.5%), aggression (five subjects, 9.6%), nasopharyngitis (five subjects, 9.6%), and otitis media (five subjects, 9.6%). There were 47 AEs reported for 24 (46.2%) subjects that were considered possibly or probably related to the investigational product. The most common possibly or probably related AEs reported were anemia (five subjects, 9.6%), somnolence (four subjects, 7.7%), and weight increased (four subjects, 7.7%). One subject died during the study; the death resulted from an SAE of systemic sepsis leading to multi-organ failure and was considered not related. Relevant medical history included sodium voltage-gated channel alpha subunit 8 mutation, patent foramen ovale, tracheomalacia, tracheostomy, gastrostomy, gastroesophageal

reflux disease, global developmental delay, cortical visual impairment, and hypotonia. Overall, 17 (32.7%) subjects had experienced a total of 37 serious TEAEs. The most frequently reported serious TEAEs were seizure (six subjects, 11.5%), status epilepticus (two subjects, 3.8%), and mental status changes (two subjects, 3.8%).

An open-label study of Cannabidiol Oral Solution, 300 mg/mL (20 mg/kg/day and 40 mg/kg/day) in pediatric patients with infantile spasms refractory to adrenocorticotropic hormone (ACTH) and vigabatrin recently was halted due to futility (Protocol INS011-15-054). However, the drug was generally well tolerated for doses up to 40 mg/kg/day. A total of nine patients were included in the safety analysis. The mean duration of exposure was 29.6 days (min, max: 5, 159). Eight patients were treated for approximately 2 weeks at 20 mg/kg/day while the patient who was a Complete Responder received 238 days of investigational (IP). She increased her dose to 40 mg/kg/day at Week 10 and continued that dose until Week 34 when she enrolled into the long-term safety study INS011-14-030 to continue treatment. Of the nine patients in the safety population, three (33%) had four events: infantile spasms (3) and sedation (1).

Insys study INS011-15-043 enrolled 24 healthy adults who received a single dose of 20 mg/kg Cannabidiol Oral Solution, 300 mg/mL as part of a food effect study (Treatment A= fasted, Treatment B= fed). Neutropenia was reported in two subjects [one fed (moderate) and one fasting (mild)]. Other AEs (all considered mild) reported in the fasting arm included diarrhea (1), dry mouth (1) and nausea (1) and events of diarrhea (2) and flatulence (1) were reported in patients in the fed arm. All diarrhea, dry mouth, flatulence, and nausea events were considered possibly related to study drug. No serious AEs or deaths were reported.

INS011-16-093 was a Phase 1, open-label, randomized, single-dose (10 mg/kg), four-treatment, four-sequence, four-period, four-way crossover food effect study of multiple formulations [sesame oil-based, 100 mg/mL (fed and fasted), MCT-based, 100 mg/mL (fed), and ethanol-containing 80 mg/mL (fed)] of Cannabidiol Oral Solution in 8 healthy adult subjects. No serious AEs or AEs that led to subject discontinuation were reported. A total of two AEs were reported during the study, both following 10 mg/kg Cannabidiol Oral Solution, 80 mg/mL, administered under fed conditions. Two subjects reported mild abdominal pain, and the Investigator judged each as possibly related to study treatment. Both AEs resolved in less than 1 day. No AEs were related to abnormal laboratory tests, vital signs, ECGs, or physical examinations.

Safety data from the food effect studies in healthy adult subjects demonstrated that the MCT formulations single dose of 20 mg/kg [Cannabidiol Oral Solution, 300 mg/mL (INS011-15-043)] and 10 mg/kg/dose [Cannabidiol Oral Solution, 100 mg/mL (INS011-16-093)] was generally well tolerated. No AEs were reported for the MCT 100 mg/mL formulation in INS011-16-093) and only eight treatment-emergent AEs were reported in INS011-15-043 [three patients fasting and four subjects fed (diarrhea and neutropenia)]. The AE of neutropenia was considered not related. Although the CBD exposure was much higher in the fed state, there was no significant difference in the number of AEs reported between fed and fasted, indicating these higher exposures did not lead to higher rates of adverse events.

The above safety data collected from five clinical studies demonstrate the CBD is generally well tolerated for doses up to 40 mg/kg/day and for durations for up to one year.

1.3.4. Efficacy in Human Epilepsy

Several preliminary studies of CBD report reductions in seizure activity for a significant subset of subjects.

In a recent report, 10 pediatric subjects (3 to 12 years of age) and one adult subject (22 years of age) showed reductions in motor seizures (generalized tonic-clonic, tonic, myoclonic, atonic) per week. Eight (73%) subjects reported a 95-100% reduction in seizure occurrence, 1 (9%) reported 75% reduction and 2 (18%) reported 20-45% reductions.[60]

In an expanded-access program in 137 patients treated with Epidiolex® (an oil-based CBD extract) in the efficacy population, they reported a median reduction in monthly motor seizures of 36.5% after 12 weeks of treatment compared to baseline.[61]

In a Phase 3 study, 120 patients with Dravet Syndrome were randomized into two treatment arms, Epidiolex® 20 mg/kg/day (n=61) and placebo (n=59). Epidiolex® or placebo was added to current anti-epileptic drug (AED) treatment regimens[62] (GW Pharmaceuticals, Dravet Syndrome study). On average, patients were taking approximately 3 AEDs, having previously tried and failed an average of more than 4 other AEDs. The average age of trial participants was 10 years and 30 percent of patients were less than 6 years of age. The median baseline convulsive seizure frequency per month was 13.

The primary efficacy endpoint was a comparison between Epidiolex® and placebo measuring the percentage change in the monthly frequency of convulsive seizures during the 14-week treatment period compared with the 4-week baseline observation period. In this study, patients taking Epidiolex® achieved a significant median reduction in monthly convulsive seizures of 39 percent compared with a reduction on placebo of 13 percent (p=0.01). The difference between Epidiolex® and placebo emerged during the first month of treatment and was sustained during the entire treatment period.

1.4. Infantile Spasms

Infantile Spasms is a devastating form of epilepsy that typically strikes children in the first year of life.[62] Usually provoked by one of many structural, genetic, or metabolic etiologies, Infantile Spasms manifests with clusters of a distinct seizure-type (spasms), and is often accompanied by an EEG pattern known as hypsarrhythmia.[63] Unsuccessful treatment, as well as delay in definitive treatment, are associated with tremendous reductions in neurodevelopmental outcome.[64] Among pharmacologic therapies for infantile spasms, hormonal therapies such as intramuscular adrenocorticotropic hormone (ACTH, Acthar®)[65,66,67] and vigabatrin (Sabril®)[68] are the most efficacious. Almost half of patients either fail first line therapy or relapse after initially successful treatment.[69] The side-effect profiles of the above therapies are poor: vigabatrin is associated with irreversible peripheral visual field defects[70,71] and the hormonal therapies impart substantial risk of immunosuppression leading to potentially lethal bacterial infections (pneumonia, sepsis, meningitis, etc.) as well as hypertension that has been associated with cardiac failure.

Accordingly, there is a tremendous need for safe and effective therapies in the treatment of infantile spasms. This need is even more pronounced in those patients who have failed currently approved therapies.

1.5. Study Rationale

Therapeutic failure may lead epilepsy patients to try alternative treatments, including "recreational drugs" and especially cannabis.[72] As summarized in Sections 1.2.1 and 1.3.2, nonclinical and clinical data show that cannabidiol has a largely favorable safety profile. However, carefully controlled efficacy and safety studies have not been done and the specific profile of Cannabidiol Oral Solution has not been examined in infantile spasms.

The primary purpose of this study is to formally investigate the efficacy and safety of Cannabidiol Oral Solution as adjunctive therapy in first-line treatment with vigabatrin to determine whether the addition of CBD will either increase the response rate associated with the use of vigabatrin alone or reduce the incidence of relapse.

1.6. Summary of Potential Risks and Benefits

As discussed in Sections 1.2 and 1.3, numerous nonclinical and clinical studies have examined other formulations of CBD. Several areas of potential concern have been identified with the use of CBD, especially in nonclinical studies. These include:

- Competitive binding of CYP proteins (thus, an impact on drug metabolism in the liver).
    - Cannabidiol is metabolized predominantly by CYP3A4 and CYP 2C19. Cannabidiol may inhibit these two isozymes, as well as having small effects on CYP3A5, CYP1A1, and CYP2C9.
- Abnormal spermatogenesis.
- Abnormal induction of FSH in males.
- Potential downregulation of immune responses involving the T, B, T-helper, and T cytotoxic subsets of leukocytes and/or those dependent on IL-2 or IFN-γ.

Based on recent studies of cannabinoid administration in humans, controlled CBD may be safe in humans and animals. However, further studies are needed to clarify these reported in vitro and in vivo side-effects.[20]

A Phase 1/2 study to assess the pharmacokinetics and safety of multiple doses of pharmaceutical-grade synthetic Cannabidiol Oral Solution in 61 pediatric subjects with treatment-resistant seizure disorders who were between <2 years of age to 17 years of age was conducted by Insys (Protocol INS-011-14-029). Steady-state levels of cannabidiol appeared to be attained with approximately 2 to 6 days of repeated BID dosing with Cannabidiol Oral Solution, with geometric mean AUC ($_{0\text{-tau}}$) of 507.0 (Cohort 1 [10 mg/kg/day,]) 836.0 (Cohort 2 [20 mg/kg/day]), and 2108 ng·h/mL (Cohort 3 [40 mg/kg/day]) for all age categories combined. All doses of Cannabidiol Oral Solution from 10 mg/kg/day up to 40 mg/kg/day in divided doses were generally well tolerated. There were no clinically relevant differences in the AE profile among patients in the infant, child, and adolescent age categories. The majority of patients reported ≥1 TEAE (most commonly in the system organ classes of gastrointestinal disorders and nervous system disorders).

The inclusion/exclusion criteria, concomitant medication guidelines, and safety monitoring (AEs, clinical laboratory, vital signs, and physical examination assessments) planned for this study are intended to minimize these potential safety risks.

Criteria for removal of subjects from the study will dictate discontinuation of subject participation should a safety issue arise (see Section 3.3).

Two facets of the current treatment landscape for pediatric patients with infantile spasms support the potential benefit for patients in this study. First, as reviewed in Section 1.4, newly diagnosed pediatric patients when treated with either ACTH or vigabatrin experience a significant unmet medical need despite ongoing treatment because of the limited response rate or the incidence of relapse. This study is expected to serve as a critical step in the development of Cannabidiol Oral Solution as an adjunctive treatment for pediatric patients who are initially diagnosed with infantile spasms.

Second, pharmaceutical grade synthetic Cannabidiol Oral Solution is expected to have several distinct advantages over cannabis plant-derived extracts:

- Availability of the drug substance does not depend on cannabis plant production.
  - As such, the development of Cannabidiol Oral Solution will not support growth and distribution of plants from which marijuana is derived.
- Manufacture of Cannabidiol Oral Solution does not involve an extraction process whereby the derived constituents could also include a significant amount of Δ^9-THC.
  - The manufacturing process can be controlled so that mass quantities can be produced that are uniform in quality, purity, and consistency and can be delivered in known and predetermined quantities.
- Variability in concentration and constituents should be reduced among batches, which may improve safety and tolerability.
- Reduced concern for contamination by Δ^9-THC, herbicides, pesticides, etc.

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 Cannabidiol Oral Solution after the 14-day treatment with vigabatrin or vigabatrin plus Cannabidiol Oral Solution is complete.
- 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. INVESTIGATIONAL PLAN

3.1. Overall 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 occur during Visit 2 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

Approximately, 190 patients in total will be enrolled into one of the two treatment arms; 130 patients in the investigational product arm with 60 patients in the placebo arm. Patients will be dosed approximately every 12 hours with meals to help ensure consistent plasma levels are achieved and to reduce variability.

Doses of CBD exceeding 40 mg/kg/day will not be examined in this study. In addition to the safety assessments required by the study protocol, the investigator will monitor patients throughout the study as recommended in the approved product label for vigabatrin. Study participants will be newly diagnosed pediatric patients age 1 to 24 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 140 days.

The study design and patient progression through the study is outlined in Figure 1. All screening, efficacy, and safety evaluations will be performed according to the schedule of assessments summarized in Table 1.

Each newly diagnosed patient with Infantile Spasms will complete a Screening Period and will have up to 14 days to enroll in the study.

Patients will have a, 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 and a 24-hour video EEG at Visit 5 (Day 14 to Day 15) of the Initial Treatment Period to establish their final level of infantile spasms and hypsarrythmia. A blinded central reader, not involved in the study, will evaluate the video EEGs and determine responder status. Details of the video EEG assessment will be provided in the video-EEG Charter. The treatment response categories are summarized in Table 2. In addition, a 9-hour video EEG will be conducted during the Extended Treatment Period to confirm parent/caregiver report of relapse. If possible, a 9-hour video EEG will be conducted for patients who have continued into the Extended Treatment Period and decided to Early Withdraw. A video EEG is not required for patients who decide to withdraw during the Initial Treatment Period.

Table 2: Video EEG Response Definitions

Response Category	Definition
Complete Response	Complete resolution of spasms and hypsarrythmia confirmed by video EEG
Partial Response	Complete resolution of either spasms or hypsarrythmia confirmed by video EEG
Non-Response	No improvement or worsening of spasms/hypsarrythmia burden

3.1.1. Initial Treatment Period

- Day 1 (Visit 2): Patients will receive the initial 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 BID for 3 days.
- 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, concomitant medications, height/weight, and assess adverse events (AEs). For those patients who tolerate the initial dose, the dose for vigabatrin will be increased to 100 mg/kg/day BID, and either CBD 30 mg/kg/day and matching CBD placebo 10 mg/kg/day, or matching CBD 40 mg/kg/day BID placebo for 3 days.
- Day 7 (Visit 4): Patients will return to the study center to evaluate medical status (seizure diary, vital signs, and neurological exam), clinical laboratory assessments, concomitant medications, height/weight, and assess AEs. For those patients who tolerate the increased doses, the dose of vigabatrin will be increased to 150 mg/kg/day and CBD or CBD placebo to 40 mg/kg/day for the remaining 9 days. Vigabatrin, CBD, and matching placebo will be administered in a twice daily fashion at 12-hour intervals with meals.

As part of their standard of care, investigators will assess safety and tolerability of the treatment regimens throughout the study period. All subjects will continue on their treatment until confirmation from the central reader on the 24-hour video EEG and clinical laboratory results are received.

3.1.2. Extended Treatment Period

Following the Initial Treatment Period:

- Complete Responders will continue receiving their assigned treatments of vigabatrin plus either CBD 40 mg/kg/day or placebo for 75 days, until Week 13 (Day 90), to monitor progress for treatment response.
- During the Extended Treatment Period, the investigator may reduce the dose of CBD or CBD placebo to 30 mg/kg/day for safety or tolerability. If the subjects cannot tolerate the 30 mg/kg/day, the drug will be discontinued and the patient withdrawn from the study following the completion of the taper period.

3.1.3. Partial Responders

- Partial responders will be offered the opportunity to enroll in an open-label safety study that allows investigators to combine standard-of-care treatment with CBD.

3.1.4. Taper Period

Following the completion of the Initial Treatment Period (Visit 6), partial responders who do not enroll in the open-label safety study and non-responders will have vigabatrin and CBD tapered as follows:

- Vigabatrin taper: 150 mg/kg/day will be reduced to 100 mg/kg/day for 3 days, then the 100 mg/kg/day dose will be reduced to 50 mg/kg/day for 3 days, and then discontinued.
- CBD or CBD Placebo taper: 40 mg/kg/day will be reduced to 30 mg/kg/day for three days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for 3 days, and then discontinued.

Complete Responders will be tapered off vigabatrin and CBD or CBD placebo at the completion of the Extended Treatment Period, and all patients will be tapered off at any Early Withdrawal Visits, using the same schedules as described above.

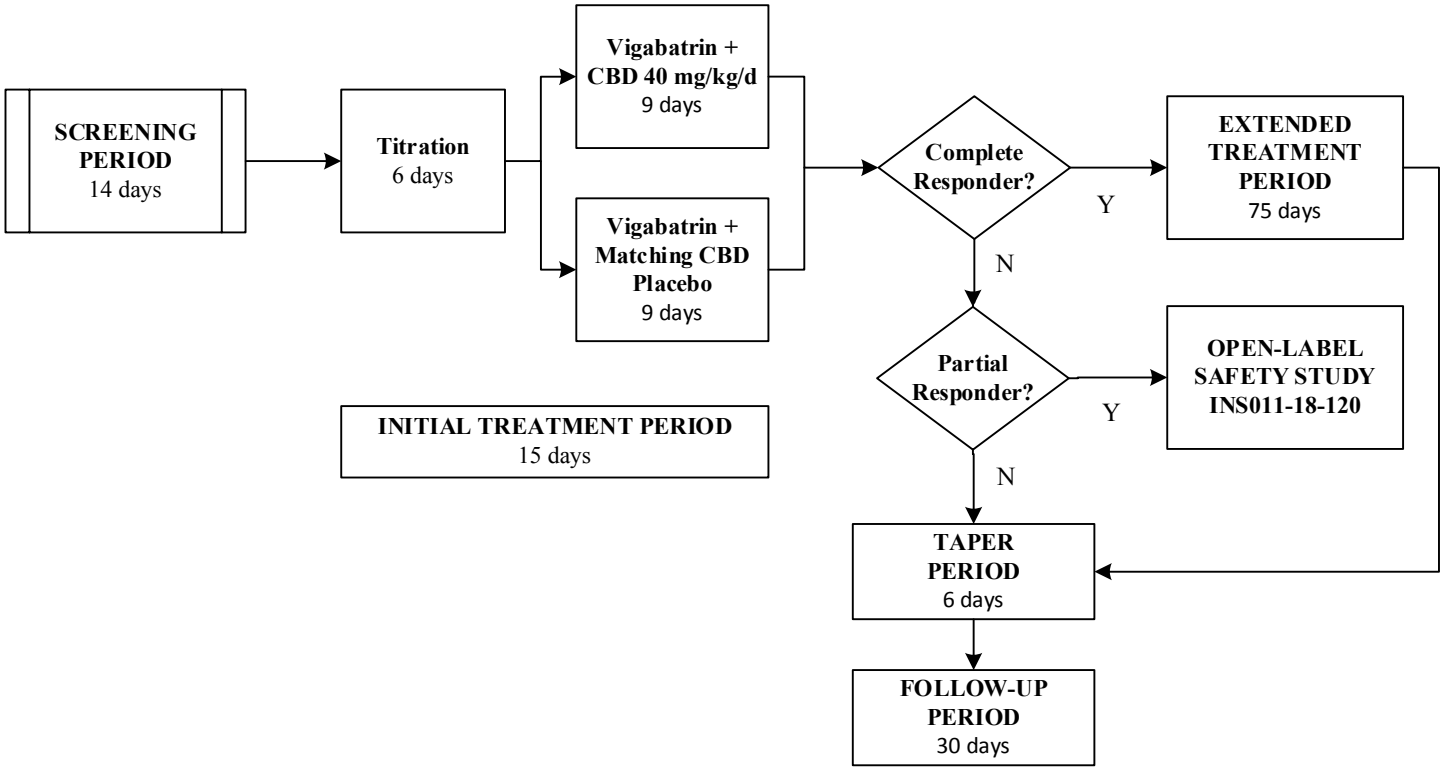
If the investigator decides to continue vigabatrin as a treatment for patients after the end of study or early withdrawal, tapering of vigabatrin will be left to the discretion of the PI.

CBD requires tapering off at the End of Study or at the Early Withdrawal visit.

3.1.5. Follow-up Period

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

Figure 1: Study Design Schematic



3.2. Patient Selection

Each patient must satisfy all of the following inclusion and exclusion criteria.

3.2.1. Inclusion Criteria

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 1 months to 24 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)] and hypsarrythmia) obtained during the Screening Period and read by a central reader.
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.
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. Patient currently on any disallowed CYP3A4-related medication listed in Appendix 1 (phenytoin, fluvoxamine, carbamazepine, and St. John's Wort).
9. Previously received any investigational drug or device or investigational therapy within 30 days before Screening.

10. 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). The investigator may deem the patient eligible if he or she judges the laboratory values to be not clinically significant.

3.3. Removal of Patients from Therapy or Assessment

Patients will be allowed to discontinue their participation in the study at any time for any reason (withdrawal of consent).

The inclusion/exclusion criteria in Sections 3.2.1 and 3.2.2 are to be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be withdrawn from the study and the Sponsor must be contacted.

In addition, participation in this clinical study may be discontinued by the Investigator or by the sponsor for any of the following reasons:

- Intolerable side effects of the study product.
- Changes in medical status or medical condition of the patient such that the Investigator believes that patient safety will be compromised or that it would be in the best interest of the patient to stop treatment.
- Patient safety or welfare is at risk.
- Non-compliance with study visits, defined as failure to perform any portion of scheduled assessments or procedures.
- Any unforeseen event that in the opinion of the treating physician and/or the Principal Investigator, will prevent the research participant from continuing in this study.
- Sponsor decides to stop the study.

In the event of a patient's withdrawal, the investigator will promptly notify the sponsor.

Patients who withdraw from the study early will complete an Early Withdrawal Visit. Should any patient choose to withdraw early from the study, they will be advised of the safety precautions to be taken and will be followed until resolution of any AE or until the unresolved AEs are judged by the investigator to have stabilized.

If a patient discontinues the study prematurely, the investigator's impression of efficacy and tolerability of the study drug, as evaluated by the Clinical Global Impression – Global Improvement (CGI-I) assessment, will be assessed and recorded immediately before discontinuation. If possible, the parent/caregiver will be encouraged to have an Early Withdrawal visit with 9-hour video-EEG.

3.4. Dose Adjustment Criteria

During the Extended Treatment Period, the investigator may reduce the dose of CBD or CBD placebo once from 40 mg/kg/day to 30 mg/kg/day for safety or tolerability. In addition, tapering of vigabatrin and CBD will be required as described in Section 3.1.4.

3.5. Stopping Rules

The Investigator reserves the right to terminate the study in the interest of patient safety and welfare. The Sponsor reserves the right to terminate the study at any time for administrative reasons. Patients will also be discontinued when their liver enzymes and serum bilirubin reach:

- ALT or AST > 8 x ULN.
- ALT or AST > 5 x ULN for more than 2 weeks.
- ALT or AST > 3 x ULN and (TBL>2 x ULN or INR>1.5).
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

4. TREATMENTS

4.1. Treatments Administered

4.1.1. Initial Treatment Period

On Day 1 (Visit 2), patients will receive the initial 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 BID for 3 days.

Following the 3-day titration, on Day 4 (Visit 3) vigabatrin will be increased to 100 mg/kg/day [BID], and either CBD 30 mg/kg/day and matching CBD placebo 10/mg/kg/day or matching CBD 40 mg/kg/day placebo BID for 3 days.

On Day 7 (Visit 4) vigabatrin will be increased to 150 mg/kg/day plus CBD 40 mg/kg/day administered twice daily for the remaining 9 days. Placebo patients will receive CBD 40 mg/kg/day placebo BID for 15 days. All subjects will continue on their treatment at the end of study until confirmation from the central reader on the 24-hour video EEG and clinical laboratory results are received.

4.1.2. Extended Treatment Period

Following the Initial Treatment Period:

- Complete Responders will continue receiving their assigned treatments of vigabatrin plus either CBD 40 mg/kg/day or placebo for 75 days, until Week 13 (Day 90), to monitor progress for treatment response.
- During the Extended Treatment Period, the investigator may reduce the dose of CBD or CBD placebo to 30 mg/kg/day for safety or tolerability. If the subjects cannot tolerate the 30 mg/kg/day, the drug will be discontinued and the patient withdrawn from the study following the completion of the Taper Period.

4.1.3. Partial Responders

- Partial responders will be offered the opportunity to enroll in an open-label safety study that allows investigators to combine standard-of-care treatment with CBD.

4.1.4. Taper Period

Following the completion of the Initial Treatment Period (Visit 6), partial responders who do not enroll in the open-label safety study and non-responders will have vigabatrin and CBD or CBD placebo tapered as follows:

- Vigabatrin taper: 150 mg/kg/day will be reduced to 100 mg/kg/day for 3 days, then the 100 mg/kg/day dose will be reduced to 50 mg/kg/day for 3 days, and then discontinued.
- CBD or CBD Placebo taper: 40 mg/kg/day will be reduced to 30 mg/kg/day for three days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for 3 days, and then discontinued.

Complete Responders will be tapered off vigabatrin and CBD or CBD placebo at the completion of the Extended Treatment Period, and all patients will be tapered off at any Early Withdrawal Visits, using the same schedules as described above. If the investigator decides to continue vigabatrin as a treatment for patients at the end of study or early withdrawal, tapering of vigabatrin will be left to the discretion of the PI.

CBD requires tapering off at the End of Study or at the Early Withdrawal visit.

4.2. Method of Assigning Patients to Treatment Groups

Following confirmation of eligibility, patients will be randomized into one of two investigational product dose groups (vigabatrin plus CBD 40 mg/kg/day or vigabatrin plus matching placebo).

The randomization schedule will be computer generated by using a permuted block algorithm and will randomly allocate the IP to randomization numbers. The randomization numbers will be provided to the drug packager who will prepare blinded drug kits. The randomization schedule will be prepared by the sponsor or sponsor's representative before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No subject will be randomized into this study more than once.

4.3. Blinding and Unblinding Treatment Assignment

This is a double-blind study with vigabatrin, CBD, and matched CBD placebo components. Study centers will be provided with three dosage levels of CBD (20 mg/kg/day, 30 mg/kg/day, 40 mg/kg/day, and matching placebos) in identical packaging, and three dosage levels of vigabatrin (50 mg/kg/day, 100 mg/kg/day, and 150 mg/kg/day), matched with the randomization schedule for that center.

All patients and study personnel involved in the conduct of the study, including data management, will be blinded to the Initial Treatment Period.

Study personnel will endeavor to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the patient's treatment assignment. Unblinding should be discussed in advance with the sponsor, sponsor's representative, or medical monitor if possible. For emergency unblinding, study personnel will contact the sponsor or sponsor's representative. If the investigator is not able to discuss treatment unblinding in advance, then he or she must notify the sponsor, sponsor's representative, or medical monitor as soon as possible about the unblinding incident without revealing the patient's treatment assignment. The investigator or designee must record the date and reason for study unblinding in the source document for that patient. In all cases that are not emergencies, the investigator must discuss the event with the sponsor, sponsor's representative, and/or medical monitor prior to unblinding the patient's treatment assignment.

If the treatment assignment is unblinded for an individual patient, study personnel will be notified of that patient's treatment assignment without unblinding of the treatment assignments for the remaining patients in the study. Thus, the overall study blind will not be compromised. If a patient's treatment assignment is unblinded, he or she may or may not be asked to withdraw

from the study. The investigator will make this decision after consultation with the sponsor, sponsor's representative, or medical monitor.

4.4. Dose Selection Rationale

As described in Section 1.3.2, data suggest that doses up to 1500 mg/day of other formulations of cannabidiol may be safe. These dose levels were selected based on data regarding concentrations that have been administered with other cannabidiol products without significant safety concerns and accounting for the range of body weights of patients to be enrolled in this study. Additionally, doses up to 40 mg/kg/day were administered by the Sponsor in studies INS011-14-029 and INS011-14-030 and were generally well tolerated. Three infants were dosed initially with 40 mg/kg/day in INS011-14-029 and continued on the same dose in INS011-14-030, which was a 48-week, long-term safety study. Two of four infants who received 20 mg/kg/day in INS011-14-029 titrated their dose from 20 mg/kg/day up to 40 mg/kg/day and continued receiving this dose throughout the long-term safety study. No infants had dose reductions in INS011-14-029, INS011-14-030, or INS011-15-054, the double refractory infantile spasms study. Thus, whether the dose was provided with or without titration, all infants generally tolerated the 40 mg/kg/day dose. Thus, these same doses will be administered in this study.

4.5. Selection and Timing of Dose for Each Patient

Patients will receive vigabatrin and CBD or CBD Placebo twice daily during the 15-day Initial Treatment Period as described in Section 4.1. Subsequently, Complete Responders will receive CBD or CBD Placebo and/or vigabatrin twice daily during the 75-day Extended Treatment Period.

The date and time of all investigational product administrations will be documented in the case report form (CRF).

4.6. Treatment Compliance

The doses of vigabatrin and CBD or matching placebo will be administered at the study center on the days listed in Table 1 under the supervision of the investigator (or a designee). All other doses will be administered by a parent or caregiver.

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

All supplies of IP should be accounted for at the termination of the study and a written explanation provided for any discrepancies. All unused supplies and packaging materials are to be inventoried and returned by the Investigator to the Sponsor or a designee. The Investigator is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by the Sponsor or a designee.

If the study is terminated, discontinued, suspended, or completed, all unused supplies of the investigational product will be returned to the Sponsor or a designee for destruction after the final drug accountability check has been performed. Sponsor approval is required prior to drug destruction. A certificate of destruction will be provided to the Sponsor.

All regulations issued by the DEA or per local regulations in ex-US locations concerning the accountability of Schedule I medications will be followed (e.g., prevention of diversion).

4.7. Permitted and Prohibited Therapies

4.7.1. Permitted Therapies

Any medications (other than those excluded by the protocol, see Section 4.7.2) that the investigator considers necessary for a patient's welfare and will not interfere with the investigational product may be given at the Investigator's discretion.

4.7.2. Prohibited Therapies

During the Screening, Initial Treatment, Extended Treatment, Taper, and Follow-up Periods, patients are not to receive the following:

- Any cannabinoids besides the investigational drug (other formulations of CBD, Δ^9-THC, hemp oil, Realm Oil or marijuana). Exclusion criterion number 4 prohibits use within 30 days of study entry.
- Felbamate.
- Valproic acid.
- Clobazam.
- Corticotrophins.
- Medication(s) that are strong CYP3A4 inhibitors or inducers or CYP3A4-sensitive substrates with a narrow therapeutic index. A list of these medications is provided in Appendix 1.
- Systemic steroid therapy (excluding inhaled medication for asthma treatment).
- Any other investigational drug or investigational device.
- Introduction of new anti-epileptic therapies (AETs) during the study is prohibited.

Patients must refrain from consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 3 days of the first administration of investigational product and throughout the entire Treatment and Taper Periods.

Although they are not prohibited, patients taking concomitant medications may need to be monitored with special care to identify any AEs arising due to the potential for altered drug metabolism. This is discussed in detail in Section 6.2.6.9.

5. STUDY DRUG MATERIALS AND MANAGEMENT

5.1. Identity of Investigational Product

The active pharmaceutical ingredient (API) in Cannabidiol Oral Solution is a pharmaceutical-grade synthetic cannabidiol manufactured according to cGMP. It is an off-white to pale yellow resin or crystal substance that is soluble in several organic solvents with an acid dissociation constant (pKa) of 9.64. The solution is a clear, colorless to pale yellow to brown colored solution filled into a 30-mL amber glass bottle. More detailed information may be found in the IB.

5.2. Labeling and Packaging

5.2.1. Labeling

The labels for the investigational product will contain all information according to regulatory requirements.

5.2.2. Packaging

A description of the drug products may be found in Table 3. The investigational product will be supplied in 30 mL containers of a 100 mg/mL strength (i.e., 3000 mg per container).

Table 3: Description of Drug Product (20 mg/kg/day, 30 mg/kg/day, 40 mg/kg/day)

Non-proprietary or common name of drug product	Cannabidiol Oral Solution, 100 mg/mL
Dosage form	Oral solution
Strength	100 mg/mL

The investigational product will be clearly marked according to FDA and/or ICH requirements regarding use for clinical study investigation only and will be labeled with the investigational product name, study reference number, and storage conditions. It is the responsibility of the Investigator to ensure that accurate accountability records are maintained throughout the study. Study center staff will dispense the investigational product according to the handling instructions.

5.3. Dispensing and Storage

The investigational product will be stored at a controlled room temperature (20 to 25 degrees Celsius, 68 to 77 degrees Fahrenheit) or refrigerated (2 to 8 degrees Celsius, 36 to 46 degrees Fahrenheit) at the study center.

The investigational product will be dispensed from a Schedule I licensed study center. Ex- US centers must meet local regulations for dispensing investigational product. The investigator will provide study medication and exact dosing instructions to parent(s)/caregiver(s) for titration doses during Visits 2 and 3 and the full Initial Treatment Period doses during Visit 4 to be administered at home. Drug for the extended treatment period will be dispensed after clinical laboratory results and 24-hour video EEG readings have been received. Study drug will be stored at room temperature.

Cannabis and its constituents (including cannabidiol) are Schedule I controlled substances in the United States and subject to all applicable local and federal laws and regulations regarding these products. This includes security provisions for storing the controlled substances and for dispensing in a manner to prevent diversion. Additionally, the Sponsor or Investigator must provide a statement of the quantity to be manufactured and the sources of the chemicals to be used or the substance.

For US sites, the DEA regulations detail specific security requirements for storage of the investigational product. For ex-US sites, local regulations must be adhered to and IP must be securely locked in a substantially constructed cabinet. Any loss in investigational product must be reported to the Sponsor. Licensed practitioners must store controlled substances in a "securely locked, substantially constructed cabinet" and must notify the DEA of the theft or significant loss of any controlled substances within 1 business day of discovering such loss or theft. Furthermore, all practitioners are prohibited from hiring employees who have been convicted of a drug-related felony or who have had a DEA registration denied or revoked.

Investigators are responsible for ensuring that all applicable licensures are in place and storage conditions are appropriate.

Study centers are required to provide complete information, including CRFs and final outcomes, on all instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in the amount of the clinical supplies of the investigational product, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why patients dropped out of the study.

5.4. Drug Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

All supplies of IP should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused supplies and packaging materials are to be inventoried and returned to the Sponsor or a designee by the Investigator. The Investigator is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by the Sponsor or a designee.

If the study is terminated, discontinued, suspended, or completed, all unused supplies of the investigational product will be returned to the Sponsor or a designee for destruction after the final drug accountability check has been performed. Sponsor approval is required prior to drug destruction. A certificate of destruction will be provided to the Sponsor.

All regulations issued by the DEA concerning the accountability of Schedule I medications will be followed (e.g., prevention of diversion). Ex- US centers will be required to follow local regulations.

6. STUDY ASSESSMENTS

6.1. Efficacy Assessments

To assess the efficacy of Cannabidiol Oral Solution, a 9-hour video-EEG will be completed during Screening and a 24-hour video-EEG will be performed from Day 14 (Visit 5) to Day 15. During the Extended Treatment Period, a 9-hour video-EEG will be completed to confirm parent/caregiver reports of relapse or complete resolution. If possible, a 9-hour video EEG will be conducted for patients who have continued into the Extended Treatment Period and decided to Early Withdraw. A video EEG is not required for patients who decide to withdraw during the Initial Treatment Period.

The video EEGs should include at least one full wake/sleep cycle. Video EEGs may be first read by the investigator. However, no efficacy assessment will be made based on the investigator's reading of the video EEG and this read will not be captured in the database. An Independent Central Reader will evaluate all video EEGs in a blinded manner and determine responder status for the primary endpoint. Details regarding requirements for the conduction of the video EEG and the Independent Central Reader's review and assessment of the video EEG is outlined in the EEG Charter. The treatment response categories are summarized in Table 2.

- The CGI-S will be completed by the investigator at screening.
- The CGI-I will be completed by the investigator at Visit 6 of the Initial Treatment Period, or the Early Withdrawal Visit.
- Daily seizure diaries will be completed throughout the Initial and Extended Treatment Periods, or the Early Withdrawal Visit.

If a patient discontinues the study prematurely, the investigator'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.

6.2. Safety Assessments

Safety assessments for all patients will include medical history, physical and neurological examinations, vital signs (seated or supine blood pressure [depending on patient age and ability], seated blood pressure, pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, liver enzymes, and serum bilirubin), prior medication history (assessment of past/current AETs and concomitant medications), and AE assessments. The safety assessments will be conducted for each patient at specific study Days and Visits, as indicated in Table 1. In addition to the safety assessments required by the study protocol, the investigator will monitor patients as recommended in the current FDA-approved vigabatrin prescribing information.

6.2.1. 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.

6.2.2. Physical Examinations

The first physical examination will include evaluation of general appearance, ears, eyes, nose, and throat (EENT), heart, peripheral vasculature, lungs, musculoskeletal system, abdomen, endocrine system, and skin. Height/length and weight will be obtained. Subsequent brief physical exams will consist of general appearance, height/length and weight. Head circumference will be collected.

6.2.3. Neurological Examinations

A complete neurological examination will be performed at Screening, Visit 6, Visit 9 and Early Withdrawal. This exam will include mental status, visual assessment, nystagmus, cranial nerves, motor and sensory systems, reflexes coordination and gait (if applicable based on age). A brief neurological exam will be completed at all other visits; this will not include a visual assessment. On Day 4 (Visit 3), and Day 7 (Visit 4) a brief neurological examination will be performed predose and approximately 2 hours following administration of the morning dose of the investigational product. If needed, additional visual assessments, may be performed based on the clinical recommendations for patient's treatment with vigabatrin.

6.2.4. 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.

Additional vital sign measurements may be performed as deemed medically necessary by research personnel.

6.2.5. Clinical Laboratory Assessments

6.2.5.1. 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.

6.2.5.2. Chemistry

Blood samples for the following serum chemistry assessments: albumin, blood urea nitrogen (BUN), creatinine, total and direct bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na^+), potassium (K^+), chloride (Cl^-), lactate dehydrogenase (LDH), uric acid, glucose, and calcium.

6.2.6. Adverse Events and Serious Adverse Events

6.2.6.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product.

Patients will be monitored throughout the study for AEs. Monitoring for treatment-emergent AEs (TEAEs) will begin as soon as the patient is dosed. All AEs must be followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted. The investigator should use their discretion in ordering additional tests as necessary to monitor the progress of such events.

An AE may be:

- A new illness, not documented in the patient's medical history;
- Worsening of a concomitant illness;
- An effect of the study medication; it could be an abnormal laboratory value, as well as a significant shift from baseline within normal range which the qualified investigator or medical qualified designate considers to be clinically important;
- A combination of two or more of these factors.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

Seizures or worsening seizures are not considered AEs as they are considered part of the underlying disease. Injuries that occur as a result of a seizure, such as a broken nose, and new seizure types will be considered adverse events.

Patients will be monitored throughout the study for AEs. All AEs must be followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted. The investigator should use his/her discretion in ordering additional tests as necessary to monitor the progress of such events.

Adverse events reported prior to dose administration will be recorded as part of the patient's medical history.

6.2.6.2. Classification of Adverse Events

Adverse events are to be recorded on the AE page of the patient's case report form (CRF). Severity will be graded according to the following definitions:

- Mild: The patient experiences awareness of symptoms but these are easily tolerated or managed without specific treatment.
- Moderate: The patient experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment.
- Severe: The patient is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures.

6.2.6.3. Causality: Drug Relationship Assessment

The relationship of the event to the study drug should be determined by the investigator according to the following criteria:

- Definitely related: The event follows a reasonable temporal sequence from the time of drug administration that cannot be explained, follows a known or expected response pattern to the study drug, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.
- Probably related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.
- Possibly related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.
- Unlikely related: The event follows little or no temporal sequence from the time of drug administration that makes a causal relationship improbable and/or other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs is a more likely alternative.
- Not related: The event is most likely produced by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely.

6.2.6.4. Definition of Serious Adverse Events

A serious AE (SAE) is any AE that fulfills any of the following criteria, as per 21 CFR 312.32:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is medically significant or requires intervention to prevent one of the outcomes listed above.

Serious AEs will be captured from the time of consent through the end of the study.

6.2.6.5. Actions Taken

Actions taken may consist of:

- None
- Study drug discontinued
- Dose modified
- Required concomitant medication
- Required procedure
- Other

6.2.6.6. Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Death
- Unknown

6.2.6.7. Adverse Event Recording and Reporting

Adverse events will be recorded throughout the study in the source documents and in the CRFs. The investigator will rate AEs for seriousness, intensity, causality, action taken, and outcome as described in the previous section.

Expedited reporting is required for serious unexpected adverse drug reactions. Fatal or life-threatening unexpected drug reactions must be reported by the Sponsor to regulatory agencies no more than 7 days after the Sponsor's first knowledge of the reaction; followed by as complete a report as possible within 8 additional days. Unexpected adverse drug reactions must be reported no later than 15 days after the Sponsor's first knowledge of the reaction. In order to comply with these requirements, the investigator or delegate must inform the Sponsor immediately upon occurrence of any SAE. The site will complete the SAE Report Form as thoroughly as possible and e-mail it to WCT within 24 hours of the investigators first knowledge of the event.

These SAE reports must contain the following information:

A. Study name/number

B. Study drug

C. Investigator details (name, phone, fax, e-mail)

D. Patient number

E. Patient initials

F. Patient demographics

G. Clinical event

1) Description
2) Date of onset
3) Treatment (drug, dose, dosage form)
4) Adverse event relationship to study drug
5) Action taken regarding study drug in direct relationship to the AE

H. If the AE was fatal or life-threatening

I. Cause of death (whether or not the death was related to study drug)

J. Autopsy findings (if available)

The Sponsor or its representative will be responsible for notification to regulatory agencies.

6.2.6.8. Adverse Event Follow-Up

All non-serious AEs that are not related or unlikely to be related to study treatment will be followed until the end of study participation. All SAEs or AEs that are considered as possibly, probably, or definitely related to treatment will be followed until resolution or stabilization.

6.2.6.9. Monitoring of AEs Potentially Related to Drug Metabolism

Cannabidiol inhibits drug metabolism mediated by a subset of CYP proteins (see Section Section 1.1.2). Thus, the Investigator and study center staff should monitor patients who are taking concomitant medications that are metabolized by CYP2C19, CYP2C9, CYP3A4, CYP1A2 or by P-glycoprotein with special care. Medication(s) that is/are strong inhibitor(s) or inducer(s) or sensitive substrates of CYP3A4 are exclusionary and prohibited (see Sections 3.2.2 and Section 4.7.2). However, patients taking medications that are weak inhibitors or inducers of CYP3A4 should be monitored with special care.

6.2.6.10. Data Monitoring Committee

The Data Safety Monitoring Committee (DSMC) will consist of a least one physician with experience in treating IS subjects and at least one biostatistician. The DSMC ensures that the ethical principles are observed and monitors the safety of the subjects. To fulfil its responsibilities, the DSMC may have access to the clinical data. The DSMC may also meet on an ad hoc basis if needed. The DSMC will be informed to what extent the data and analyses provided to them have been quality controlled. Members of the DSMC will not be involved in other study-related tasks. The DSMC procedures are described in the Data Monitoring Committee Charter.

6.3. Pharmacokinetics Assessments

A blood sample for PK analysis of CBD and 7-OH-CBD will be obtained on Day 15 just prior to the second dose during the 24-hour video EEG. Whole blood will be obtained in a Vacutainer® tube containing K2-EDTA as a preservative.

7. STUDY PROCEDURES

The assessments and procedures that will be conducted during this study are summarized in Table 1.

7.1. Screening Period (Visit 1)

Potential study patients will be examined before the start of the study to determine their eligibility for participation. Prior to performing any study related procedures or assessments, the Investigator will ensure that the patient's legal representative (parent[s]/caregiver[s]) provides written informed consent. Patients and their parent(s)/caregiver(s) will receive a copy of the ICF for review and must provide fully informed consent prior to study participation.

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.

- Obtain written informed consent.
- Review of inclusion and exclusion criteria (see Sections 3.2.1 and 3.2.2).
- Record demographic data.
- Record recent and concomitant medication and procedure history including vitamins, herbal preparations, blood products, and over-the-counter drugs. All medications taken ≤30 days of the Screening Visit must be documented in the concomitant medications section of the CRF.
- Record all prior and current anti-epileptic therapies (AETs, including drugs, ketogenic diet, vagal stimulators etc.)
- Record medical and surgical history.
- Record the types of seizures and the frequency of infantile spasms occurring ≤28 days of the Screening Visit based on parent/caregiver recollection.
- Record vital signs (seated or supine blood pressure [depending on patient age and ability], pulse rate, respiratory rate, and temperature measurements).
- Draw blood samples for hematology and chemistry.
    - Section 7.4 details the volume of samples to be drawn based on patient age.
- Perform a complete physical examination (see Section 6.2.2), including height, weight, and head circumference.
- Perform a complete neurological examination (see Section 6.2.3).
- Perform a minimum of 9-hr video-EEG that includes a full sleep-wake cycle.
- Completion of investigator CGI-S.
- Provide daily seizure diary to capture seizure activity (infantile spasms only) between visit 1 and visit 2, and train the caregiver to recognize and capture the infantile spasms.

7.2. Assessments and Procedures

7.2.1. Initial Treatment Period

7.2.1.1. Visit 2 (Day 1)

Once the patient has been approved for the study, they will return to the study clinic where the patient will be randomized to the appropriate treatment arm. 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 at 12-hour intervals for three days.

The following procedures and assessments will be performed during Visit 2:

- Review and record seizure diary.
- Record concomitant medications
- Record AEs.
- Perform a brief neurological examination predose (see Section 6.2.3).
- Administer the first titration dose of vigabatrin and the Investigational product and train caregiver(s) to measure, administer, and record doses.
- Vital signs will be taken after approximately 5 minutes seated or supine, depending on patient ability. Vital signs should be taken predose and at approximately 4 hours postdose.

7.2.1.2. Day 2 and Day 3

- The Investigator or designee will follow up by phone or E-mail for the first three days of the Initial Treatment Period, and record any AEs.
- Administer prescribed titration dose at approximately 12-hour intervals by the parent/caregiver.
- Parent/caregiver should also complete the seizure diary.

7.2.1.3. Visit 3 (Day 4)

Patients will receive 100 mg/kg/day divided twice daily of vigabatrin and (30 mg/kg/day CBD and CBD placebo 10 mg/kg/day or matching CBD 40 mg/kg/day placebo) divided twice daily for 3 days, according to the patient's assigned cohort. the following procedures and assessments will be performed on Day 4 for all patients prior to IP administration:

- Record concomitant medications
- Record vital signs (seated of supine blood pressure [depending on patient age and ability], pulse rate, respiratory rate, and temperature)
- Record height and weight.
- Perform a brief neurological examination predose (see Section 6.2.3).

- Draw blood samples for hematology and chemistry.
  - Section 7.4 details the volume of samples to be drawn based on patient age.
- Record AEs.
- Record and review daily seizure diary.
- Administer dose of vigabatrin and investigational product

The following activities will occur after administration of the morning dose of the investigational product:

- Perform an additional brief neurological examination approximately 2 hours postdose.
- Records AEs.

Patients will be released from the study center after assessments are complete.

7.2.1.4. Visit 4 (Day 7)

Patients will receive 150 mg/kg/day divided twice daily of vigabatrin and (40 mg/kg/day CBD day or matching CBD placebo) twice daily for 9 days, according to the patient's assigned cohort. The following procedures and assessments will be performed on Day 7 for all patients prior to IP administration:

- Record concomitant medications.
- Record vital signs (seated of supine blood pressure [depending on patient age and ability], pulse rate, respiratory rate, and temperature).
- Record height and weight.
- Perform a brief neurological examination predose (see Section 6.2.3).
- Draw blood samples for hematology and chemistry.
  - Section 7.4 details the volume of samples to be drawn based on patient age.
- Record AEs.
- Record and review daily seizure diary.
- Administer dose of vigabatrin and investigational product.

The following activities will occur after administration of the morning dose of the investigational product:

- Perform an additional brief neurological examination approximately 2 hours postdose.
- Records AEs.

7.2.1.5. Days 7-15

- Patients will receive 150 mg/kg/day divided twice daily of vigabatrin and (40 mg/kg/day CBD or matching CBD placebo) from Day 7 through Day 15. Doses will be administered at approximately 12-hour intervals by the parent/caregiver.
- Parent/caregiver should complete the seizure diary daily and note any adverse events. The investigator or designee will follow up by phone or e-mail on Days 9 to 11.

7.2.1.6. Visit 5 (Day 14)

On Day 14, patients will be admitted to the study center before the morning administration of vigabatrin and the investigational product and assessments. The following assessments will be completed PRIOR to administration of the morning dose of vigabatrin and the investigational product:

- Record concomitant medications.
- Record vital signs (seated or supine blood pressure [depending on patient age and ability], pulse rate, respiratory rate, and temperature measurements).
- Record height and weight.
- Perform a brief neurological examination (see Section 6.2.3).
- Record AEs.
- Record and review daily seizure diary.
- Start meal diary collection.

. The following assessments will be completed after administration of the morning doses of vigabatrin and the investigational product:

- Start the 24-hour video EEG assessment.

7.2.1.7. Visit 6 (Day 15, End of Study for the Initial Treatment Period)

The following activities will occur on Day 15, at approximately 24 hours post the Day 14 morning dose:

- Complete the 24-hour video EEG assessment.
- Record concomitant medications and AETs
- Record vital signs (seated or supine blood pressure [depending on patient age and ability], pulse rate, respiratory rate, and temperature measurements).
- Record height and weight and head circumference.
- Perform a complete neurological examination (see Section 6.2.3).
- Draw blood samples for hematology, chemistry and PK analysis. PK analysis will be obtained on Day 15 just prior to the second dose during the 24-hour video EEG.
    - Section 7.4 details the volume of samples to be drawn based on patient age.

- Record and review daily seizure diary.
- Record AEs.
- Completion of investigator CGI-I.
- Complete meal diary collection.
- Administer dose of vigabatrin and investigational product

Patients will be discharged from the study center after assessments are complete. Subjects will continue treatment until confirmation of treatment response after 24-hour video EEG and clinical laboratory results are received.

7.2.2. Taper Period

Following the completion of the Initial Treatment Period (Visit 6), partial responders who do not enroll in the open-label safety study and non-responders will have vigabatrin and CBD or CBD placebo tapered as follows:

- Vigabatrin taper: 150 mg/kg/day will be reduced to 100 mg/kg/day for 3 days, then 100 mg/kg/day will be reduced to 50 mg/kg/day for 3days and then discontinued.
- CBD or CBD placebo taper: CBD: 40 mg/kg/day will be reduced to 30 mg/kg/day for 3 days, 30 mg/kg/day will be reduced to 20 mg/kg/day for 3 days, and then discontinued.

Complete Responders will be tapered off vigabatrin and CBD or CBD placebo at the completion of the Extended Treatment Period, and all patients will be tapered off at any Early Withdrawal Visits, using the same schedules as described above.

If the investigator decided to continue vigabatrin as a treatment for patients at the end of the study of at early withdrawal, tapering of vigabatrin will be left to the discretion of the PI.

CBD requires tapering off at the End of Study or at the Early Withdrawal visit. The following assessments will be performed during this period:

- Concomitant medications and AETs.
- Administer dose of vigabatrin and investigational product
- Record AEs.
- Record and review daily seizure diary.

7.2.3. Extended Treatment Period (Visit 7/Week 6, Visit 8/Week 10, and Visit 9/Week 13)

Following the Initial Treatment Period, Complete Responders will continue receiving their assigned treatments of vigabatrin plus either CBD 40 mg/kg/day or matching placebo for 75 days, until Week 13 (Day 90).

The following assessments and procedures will be completed at Visit 7 (Week 6), Visit 8 (Week 10), and Visit 9 (End of Study; Week 13):

- Record concomitant medications and AETs.

- Record vital signs (seated or supine blood pressure ([depending on patient age and ability)], pulse rate, respiratory rate, and temperature measurements).
- Record height, weight
- Head circumference (Visit 9, Week 13)
- Perform a brief neurological examination for Visits 7 and 8 and complete neurological exam for Visit 9 (EOS) (see Section 6.2.3)
- Record AEs.
- Administer dose of vigabatrin and investigational product
- Draw blood samples for hematology and chemistry.
    - Section 7.4 details the volume of samples to be drawn based on patient age.
- Record and review daily seizure diary.

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 (Visit 9; see Section 7.2.2).

7.2.4. Partial Responders

Partial responders will be offered the opportunity to enroll in an open-label safety study that allows investigators to combine standard-of-care treatment with CBD or up to ..

7.2.5. Early Withdrawal Visit

Should a patient's participation be terminated prior to Day 14 or Day 90 for any reason (see Section 3.3), an Early Withdrawal Visit will be completed. The following procedures will be completed:

- Record concomitant medications and AETs.
- Record vital signs (seated or supine blood pressure ([depending on patient age and ability)], pulse rate, respiratory rate, and temperature measurements).
- Record height and weight and head circumference.
- Record and review daily seizure diary.
- Perform a complete neurological examination (see Section 6.2.3).
- Complete investigator CGI-I.
- Record AEs.
- Perform 9-hour video EEG, if possible only for patients that continued into the Extended Treatment Period.
- Draw blood samples for hematology and chemistry.
    - Section 7.4 details the volume of samples to be drawn based on patient age.

All patients will begin tapering off investigational product and vigabatrin at this visit (see Section 7.2.2).

7.2.6. Follow-up Period

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

7.2.7. Follow-up of Adverse Events

Any AEs observed from the Screening Visit until the end of the study will be followed to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. All AEs that occur after the subject completed a clinical study should also be reported to the Sponsor within 30 days of the last dose of study drug.

7.3. Investigational Product PK Sample

A blood sample for PK analysis of CBD and 7-OH-CBD will be obtained while inpatient on Visit 6 (Day 15, EOS) just prior to the second dose during the 24-hour video EEG. A meal-diary will need to be completed on Visit 5 (Day 14) and Visit 6 (Day 15).

7.4. Sample Collection for Patients

The frequency for PK and safety laboratory samples has been adjusted to avoid excessive blood loss in a subset of patients. Multiple standards may be used to determine maximum acceptable blood loss in a clinical study. In this study, sample volumes will be adjusted for patients based on age to ensure that an excessive amount of blood is not removed. Two (2) metrics that are used to determine this volume are discussed below.

- As per the requirements of the Office for Human Research Protections, no more than 3 mL/kg per 8-week period should be removed.
- As per the National Institutes of Health, no more than 7 mL/kg per 6-week period should be removed.

Given the duration of this study, this effectively means that blood loss should not exceed approximately 3 mL/kg of body weight per patient for the entire study.

8. STATISTICS

The detailed descriptions of statistical analysis methods and data conventions will be in a separate document, the Statistical Analysis Plan (SAP). Any post-hoc analyses will be identified in the final clinical study report. This section presents general information about statistical considerations and concepts such as randomization, statistical power, and sample size. There will also be a brief discussion on analysis methodology, as well as some data conventions.

8.1. Study Endpoints

8.1.1. 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, confirmed by 24-hour video EEG from Day 14 to Day 15, as determined by the Independent Central Reader.

8.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints in the Initial Treatment Period of this study are:

- Percent of patients with resolution of infantile spasms as assessed by 24-hour video EEG from Day 14 to Day 15 (partial response).
- Percent of patients with resolution of hypsarrhythmia as assessed by 24-hour video EEG from Day 14 to Day 15 (partial response).
- Investigator impression of efficacy and tolerability of study drug (CGI-I) at Visit 6 (End of Study), or Early Withdrawal.
- Increase in the number of spasm-free days between Day 1 and Day 15 of the Initial Treatment Period, 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.

8.1.3. Safety Endpoints

The safety endpoints of this 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, medical history, and prior and concomitant medications, liver enzymes, and serum bilirubin.

8.2. Sample Size Determination

A total of 190 patients (130 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 60%.

8.3. Analysis Populations

Statistical analysis will be done on the following populations:

- Intent to Treat (ITT) Population: The ITT Population will include all patients who were randomized.
- Safety Population: The Safety Population will include all patients who were treated with at least one dose of the study drug. Patients will be analyzed according to the actual treatment they receive.
- PK Population: The PK Population will include all patients who were treated with at least one dose of the study drug and have at least one usable PK measurement.

8.4. Statistical Analyses

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], coefficient of variation [CV%; as appropriate], median, minimum, maximum, and geometric mean and geometric CV% [as appropriate for PK parameters]). Categorical variables will be summarized by presenting the number (frequency) and percentage in each category. Differences between treatment groups will be assessed by ANCOVA for continuous variables and a chi-square test for categorical variables. Pearson's correlation will be used to quantify the relationship between covariates of interest, and logistic regression may be used to simultaneously assess the relationship of multiple variables on treatment response (if enrollment provides sufficient sample size). Time to Relapse will be described with Kaplan-Meier Curves and treatment groups compared with a log-rank test.

8.4.1. Study Patients and Demographics

8.4.1.1. Disposition and Withdrawals

The numbers of patients randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by treatment group. The number of patients in each analysis population will be reported.

8.4.1.2. Protocol Deviations

Protocol deviations will be identified and listed.

8.4.1.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for the safety populations.

Demographic and baseline characteristics (including sex, age, gender, ethnicity, race, height/length, and weight) will be summarized by descriptive statistics. No formal statistical analyses will be performed. Medical history and clinical laboratory test results will be listed.

Prior and concomitant medications will be summarized by the number and percentage of patients taking each medication. They will also be classified by using the World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes and preferred terms.

8.4.2. Exposure and Compliance

The exposure to study medication will be summarized by descriptive statistics.

8.4.3. Efficacy Analyses

A 9-hour video EEG will be conducted during the Screening Period (Baseline) and a 24-hour video EEG will be conducted from Day 14 to Day 15 of the Initial Treatment Period. In addition, to confirm parent/caregiver report of relapse or complete resolution a 9-hour video EEG will be conducted during the Extended Treatment Period. For each video EEG, the number of spasms will be counted and the presence of hypsarrhythmia determined. Change from Baseline for each measure will be summarized by the median difference. Patients will be defined as having Complete Response, Partial Response, or Non-Response on Day 15 as defined in Table 2, the percentage of patients who achieve a Complete Response and Partial Responders in each treatment arm will be compared using a chi-square test.

The results of the CGI-I assessments will be listed and summarized by descriptive statistics as appropriate. The responses to the seizure diary will also be summarized by dose level and scheduled time point. All efficacy summaries will be based on the ITT Population.

Details of these summaries will be provided in the SAP. For all inferential statistical tests, a 2-sided type I error rate of 0.05 will be used throughout.

For the secondary efficacy endpoints, to maintain the trial-wise type I error rate at 0.05, a fixed sequence multiple comparisons correction with fallback will be used. The assignment of alpha levels to hypotheses being tested will be specified in the SAP.

For endpoints that are continuous in nature number, the number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive statistics. For inferential statistics:

- If the normality assumption is met, analysis of covariance (ANCOVA) using the baseline value as a covariate will be used.
- If the normality assumption is not met, a rank-ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data or other non-parametric methods will be used.
- Time to event analyses will be described with Kaplan-Meier curves and treatment groups compared with log-rank tests.

For endpoints that are categorical in nature, frequency, counts, and percentages will be presented as descriptive statistics, and a chi-square test will be used for inferential statistics.

8.4.3.1. Primary Efficacy Analysis

- Percent of patients with complete resolution of both infantile spasms and hypsarrhythmia at Day 15 (complete response) will be compared between vigabatrin plus placebo and vigabatrin plus CBD 40 mg/kg/day groups using a chi square test.

8.4.3.2. Secondary Efficacy Analyses

- 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 a chi-square test. Time to relapse will be described with Kaplan-Meier curves and treatment groups compared using a log-rank test.

- Percent of patients with complete resolution of infantile spasms at Day 15 will be compared between treatment groups using a chi-square test.
- Percent of patients with complete resolution of hypsarrhythmia at Day 15 using a chi-square test.
- Investigator impression of efficacy and tolerability of study drug (Clinical Global Impression – Global Improvement [CGI-I]) will be compared between treatment groups using ANCOVA with baseline CGI-S as a covariate.
- Percent reduction in spasm-free days between the Initial Treatment Period and Screening Period will be compared between treatment groups using ANCOVA with the baseline score as a covariate.

Secondary efficacy analyses for patients with a complete response during the Initial Treatment Period who continue to the Extended Treatment Period:

- Percent of patients who relapse during the Extended Treatment Period confirmed by video EEG following parent report of relapse.
- Time to relapse.

8.4.4. Safety and Tolerability 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.

8.4.4.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA, version 20.0) will be used to classify all AEs. Adverse event summaries will include only treatment-emergent AEs (TEAEs) by treatment group. Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened during the indicated treatment phase.

The number and percentage of patients with TEAEs will be summarized by system organ class (SOC) and preferred term (PT). Summaries of AEs by severity and relationship to the study treatment will also be provided. Serious adverse events (SAEs) and AEs resulting in discontinuation will be summarized separately in a similar manner. Patient listings of AEs and SAEs will be produced.

8.4.4.2. Clinical Laboratory Evaluations

For the continuous laboratory parameters, descriptive statistics will be presented for values collected at Screening, Initial and Extended Treatment, and End of Study/Early Withdrawal Visits, and for the changes from baseline to End of Study/Early Withdrawal.

8.4.4.3. Vital Signs

For blood pressure, pulse rate, temperature, and respiration rate, descriptive statistics will be presented for values collected at Screening, Initial and Extended Treatment, End of Study /Early Withdrawal, and Follow-up Visits, and for the changes from baseline to End of Study /Early Withdrawal.

8.4.4.4. Neurological Examination Findings

Brief neurological examinations will be presented as the number and percentage of patients that have normal or abnormal results at Screening (complete exam), Initial and Extended Treatment, End of Study, Visit 6 and Visit 9 (complete exam), Early Withdrawal (complete exam), and Follow-up Visits.

8.4.5. Pharmacokinetic Analyses

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

8.4.6. Missing Data

There will be no imputation of the missing values. Patients without a video EEG assessment on Days 14-15 will be considered non-responders for all EEG-related endpoints. Percentage of spasm-free days will be calculated based on the number of entries (up to 15 days per measurement period). 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.

9. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

9.1. Sponsor and Investigator Responsibilities

9.1.1. Sponsor Responsibilities

The sponsor, and/or sponsor's representative is obligated to conduct the study in accordance with strict ethical and data privacy principles. The sponsor reserves the right to withdraw a patient from the study, to terminate participation of a study site at any time, and/or to discontinue the study.

The sponsor, or sponsor's representative, agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

9.1.2. Investigator Responsibilities

By signing the Investigator's Agreement, the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International Conference on Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. Furthermore, the investigator agrees to abide by the EU General Data Protection Regulations. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, IPs, and their specific duties within the context of the study. Investigators are responsible for providing Insys with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

9.2. Site Initiation

Study personnel may not screen or enroll patients into the study until after receiving notification from the sponsor or sponsor's representative that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

- The study site has received the appropriate institutional review board (IRB) approval for the protocol and the appropriate informed consent form.
- All regulatory documents have been submitted to and approved by the sponsor or sponsor's representative.
- The study site has a clinical trial agreement in place.

9.3. Screen Failures

Patients who fail inclusion and/or exclusion criteria may be re-screened based on prior investigator and Sponsor approval.

9.4. Study Documents

All documentation and material provided by the sponsor, or sponsor's representative for this study are to be retained in a secure location and treated as confidential material.

9.4.1. Investigator's Regulatory Documents

The regulatory documents must be received from the investigator and reviewed and approved by the sponsor or sponsor's representative before the study site can initiate the study and before the sponsor, or sponsor's representative, will authorize shipment of IP to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location.

Additional documents, including a copy of the protocol and applicable amendment(s), the IB, CRF/electronic case report form (eCRF) completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

9.4.2. Case Report Forms

By signing the Investigator's Agreement (Section 13), the investigator agrees to maintain accurate CRFs/eCRFs and source documentation as part of the case histories for all patients who sign an informed consent form (ICF).

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor, or sponsor's representative, will provide the necessary training on the use of the specific CRFs/eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, CRF/eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the CRF/electronic data capture (EDC) system according to the completion guidelines provided by the sponsor, or sponsor's representative.

9.4.3. Source Documents

All information recorded in the CRF/EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select CRF/eCRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files. Clinical laboratory data required by the protocol will be electronically transferred from the local laboratory to the sponsor or the sponsor's representative. A paper copy of the laboratory results will be provided to the study site and should be retained with each patient's source data.

All documents pertaining to the study, including a copy of the approved protocol, copy of the ICD, completed CRFs, source documents, drug accountability and retention records, and other study related documents will be retained in the permanent archives of the study site. These will be available for inspection at any time by the Sponsor or the FDA. Per 21 CFR 312, record retention for this study is required for a period of two years following the date on which this study agent is approved by the FDA for the marketing purposes that were the patient of this investigation; or, if no application is to be filed or if the application is not approved for such indication, until two years following the date on which the entire study is completed, terminated, or discontinued, and the FDA is notified.

The investigator will provide direct access to source data and documents for trial related monitoring, audits, IEC/IRB review, and regulatory requirements.

9.5. Data Quality Control

9.5.1. Monitoring Procedures

The investigator will permit the site monitor to review trial data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory. The investigator will access medical records for the monitor to verify CRF entries. The investigator, as part of his or her responsibilities, is expected to cooperate with the sponsor or its designee in ensuring the trial adheres to GCP requirements. The investigator may not recruit patients into the study until such time that a site visit has been conducted.

9.5.2. Data Management

The CRO will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the CRO's standard operating procedures (SOPs). A comprehensive Data Management Plan will be developed including a data management overview, database contents, annotated CRF and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

The sponsor will review all data reported in CRFs of all patients before database lock. The data review meeting determines whether or not all enrolled patients can be included in the analysis

population according to the specified definition of analysis populations and evaluates whether or not medical decisions of the Investigator were appropriate for important data affecting the safety and efficacy endpoint.

9.5.3. Quality Assurance/Audit

This study will be subject to audit by the sponsor, CRO, or designee.

The sponsor or sponsor's representative may conduct audits on a selection of study sites, requiring access to patient notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify sponsor or sponsor's representative immediately.

9.6. Study Termination

The study may be terminated at the sponsor's discretion at any time and for any reason. Study sites may be asked to have all patients currently participating in the study complete all of the assessments for the telephone follow-up call.

In the event of study discontinuation, study sites may be asked to have all patients currently participating in the study complete all of the assessments for the Early Withdrawal Visit.

9.7. Study Site Closure

At the end of the study, all study sites will be closed. The sponsor or sponsor's representative may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines.
- Inadequate patient enrollment.

9.7.1. Record Retention

The investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until the following occur:

- At least 2 years after the last marketing authorization for the investigational product (IP) has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

Insys will keep personal data for no longer than reasonably necessary for our ongoing course of study, regulatory filing, and for record keeping purposes and in case of any legal claims of complaints.

Furthermore, EU citizens of residents have the following rights under the GDPR (unless subject to an exemption):

- The right to request a copy of your personal data which Insys holds about you
- The right to request that Insys corrects any personal data if it is found to be inaccurate or out of date
- The right to request your personal data is erased where it is no longer necessary for Insys to retain such data
- The right to withdraw your consent to the processing at any time
- The right to request that Insys provide you, as the data subject, with your personal data and where possible, to transmit that data directly to another data controller
- The right, where there is a dispute in relation to the accuracy or processing of your personal data, to request a restriction is placed on further processing
- The right to lodge a complaint with governmental agencies or Data Protection Authorities as provided for in the GDPR.

9.7.2. Pharmacokinetic/Laboratory Sample Retention

Laboratory samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the patient.

9.8. Changes to the Protocol

The investigator may not deviate from the protocol without a formal protocol amendment established and approved by the appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the patient or when the change involves only logistical or administrative aspects of the study. Any deviation may result in patient withdrawal from the study and rendering that patient not available for data evaluation.

The Investigator or sub-investigator should document any deviation from the protocol and the reason. If the Investigator performs a deviation from the protocol or a change of the protocol to eliminate an immediate hazard(s) to patients, the record should be immediately submitted to the sponsor, the Clinical Research Unit (CRU), and the IRB by the Investigator. The IRB will provide expedited review and approval. After the Investigator has obtained approval of the IRB, the Investigator should obtain written permission of the CRU and written agreement of the sponsor.

9.9. Financial Disclosure

These issues will be addressed in a separate agreement between the sponsor and the Investigator.

The US FDA Financial Disclosure by Clinical Investigators (21 Code of Federal Regulations [CFR] 54) regulations require sponsors to obtain certain financial information from investigators

participating in covered clinical studies; each investigator and sub-investigator is required to provide the required financial information and to promptly update Insys Development Company, Inc., with any relevant changes to their financial information throughout the course of the clinical study and for up to one year after its completion. This rule applies to all investigators and sub-investigators participating in covered clinical studies to be submitted to the FDA in support of an application for market approval.

10. REGULATORY AND ETHICAL CONSIDERATIONS

10.1. Regulatory Authority Approval

The investigator will ensure that the protocol and consent forms are reviewed and approved by the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) prior to the start of any study procedures. The IEC/IRB will be appropriately constituted and will perform its functions in accordance with Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) good clinical practice (GCP) guidelines, and local requirements as applicable.

In addition, the IRB will approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures, written information to be provided to the patients, available safety information, information about payment and compensation available to patients, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority, as applicable.

The Investigator will supply documentation to the Sponsor or designee of required IRB/IEC annual renewal of the protocol, and any approvals of revisions to the consent form, or amendments to the protocol.

10.2. Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki and GCP according to ICH guidelines. Specifically, the study will be conducted under a protocol reviewed by an IRB or IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

10.3. Statement of Investigator/Delegation of Authority

As a condition for conducting the clinical investigation, the Principal Investigator will sign the FDA Form 1572, Statement of Investigator (21 Code of Federal Regulations [CFR] Part 312).

The Principal Investigator will ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The qualified investigator will maintain a list of sub-investigator and other appropriately qualified persons to whom to delegate significant trial-related duties. Should the qualified investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

10.4. Patient Informed Consent

The Investigator is responsible for ensuring that informed consent is obtained from each parent/caregiver or legal representative and for obtaining the appropriate signatures and dates on

the consent form form (if applicable) prior to the performance of any protocol procedures and prior to the administration of study medication.

The investigator or his/her designee will inform the parent/caregiver or legal guardian of all aspects pertaining to their participation in the study. The process for obtaining informed consent will be in accordance with all applicable regulatory requirements (e.g., CFR Part 50 and ICH E6 Section 4.8). The investigator or his/her designee and the parent/caregiver or legal guardian must both sign and date the informed consent document (ICD) before the patient can participate in the study. The parent/caregiver or legal guardian will receive a copy of the signed and dated form, and the original will be retained in the site's study records. The decision to participate in the study that is made by the parent/caregiver or legal guardian is entirely voluntary. The investigator or his/her designee must emphasize to the parent/caregiver or legal guardian that consent for study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled. If the ICD is amended during the study the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICD by the IEC/IRB, and use of the amended form, including the necessity of re-consenting ongoing patients.

10.5. Investigator Reporting Requirements

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the study at his/her site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of Insys or its delegate.

11. USE OF INFORMATION AND PUBLICATION POLICY

11.1. Use of Information

All information concerning Cannabidiol Oral Solution and Insys Development Company's operations, such as Insys' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Insys Development Company and not previously published, is considered confidential information.

This confidential information shall remain the sole property of Insys Development Company, shall not be disclosed to others without the written consent of Insys Development Company, and shall not be used except in the performance of this study.

The investigator will maintain a confidential patient identification code list of all patients enrolled in the study (by name and patient number). This list will be maintained at the site, and will not be retrieved by Insys.

11.2. Publication Policy

Insys Development Company, Inc. will retain ownership of all data. All proposed publications based on this study will be subject to the sponsor's approval requirements.

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13. INVESTIGATOR SIGNATURE PAGE

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 Patients with Infantile Spasms
PROTOCOL NUMBER:	INS011-16-082
PHASE OF STUDY:	Phase 3
PROTOCOL DATE:	05 Jul 2018
STUDY SPONSOR:	Insys Development Company, Inc 1333 South Spectrum Blvd, Suite 100 Chandler, AZ 85286

PRINCIPAL INVESTIGATOR COMMITMENT:

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312.60 through § 312.70, 21 CFR § 11, 50, 54, 56) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

Principal Investigator Printed Name

Principal Investigator Signature **Date**

APPENDIX 1. CYP3A4-RELATED PROHIBITED MEDICATIONS

Example of prohibited medications (list is not exhaustive).

1. Strong inhibitors
    - Boceprevir
    - Clarithromycin
    - Conivaptan
    - Valproic acid
    - Grapefruit juice
    - Indinavir
    - Itraconazole
    - Ketoconazole
    - Lopinavir/ritonavir
    - Mibefradil
    - Nefazodone
    - Nelfinavir
    - Posaconazole
    - Saquinavir
    - Telaprevir
    - Telithromycin
    - Voriconazole
2. Strong inducers
    - Avasimibe
    - Carbamazepine
    - Phenobarbital
    - Phenytoin
    - Rifampin
    - St. John’s Wort
3. Sensitive substrates with a narrow therapeutic index
    - Alfentanil
    - Astemizole
    - Cisapride

- Cyclosporine
- Dihydroergotamine
- Ergotamine
- Fentanyl
- Pimozide
- Quinidine
- Sirolimus
- Tacrolimus
- Terfenadine