CLINICAL TRIAL PROTOCOL

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

Protocol Number: INS011-17-103
Final Protocol Date: 06 May 2019
Version: 7.0
Investigational Product: Cannabidiol Oral Solution
IND Number: IND 123,120

ClinicalTrials.gov ID: NCT03336242

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Investigational Product:	Cannabidiol Oral Solution
IND Number:	123,120
Sponsor:	Insys Development Company, Inc. 1333 South Spectrum Blvd, Suite 100 Chandler, AZ 85286
Medical Monitor:	PPD MD Insys Development Company, Inc. PPD, Clinical Development Phone: PPD Fax: PPD

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

Protocol Approved by:

PPD

Sr. Director, Clinical Operations
Insys Development Company, Inc.

PPD

Date: 15 May 2019

PPD

PPD MD
PPD , Clinical Development
Insys Development Company, Inc.

PPD PPD

Date: May 13th, 2019

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

Study center(s): Approximately 8 sites in the US.

Studied period:	**Phase of development:**
Estimated date first patient enrolled: November 2017 Estimated date last patient completed: September 2019	Phase 2

Objectives:

Primary

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

Secondary

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

Methodology:

This is a Phase 2, open-label, dose-finding study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of three doses (20, 30, and 10 mg/kg/day) of Cannabidiol Oral Solution. Doses exceeding 30 mg/kg/day will not be examined in this study.

Study participants will be pediatric patients age 3 to 17 years (inclusive) experiencing treatment-resistant childhood absence seizures who satisfy all inclusion/exclusion criteria. The study will consist of a Screening Period, a Titration Period, a Treatment Period, and a Follow-

Up Period. A total of 30 patients will be enrolled in the study. Ten patients will be enrolled in each of three dose cohorts, and no patient will participate in more than one cohort. At completion, patients will have the opportunity to enroll in an open-label long-term safety study (INS011-17-113).

Each patient will complete a Screening Period for up to 28 (± 5) days. Eligible patients will have a baseline 4-hr video-electroencephalography (video-EEG) that will include hyperventilation during their Baseline Visit. The investigator may use results of a previously obtained EEG to guide selection of the appropriate patients but the Baseline Visit video-EEG will be used for determination of eligibility and will be evaluated by an electrophysiologist not involved in the study. Details of the video-EEG assessment will be provided in the video-EEG Charter.

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

Titration and Treatment Periods

Thirty patients in total will be enrolled into one of three dose cohorts; ten patients per cohort. Patients in Cohort 1 will be treated before patients are treated in Cohort 2, and patients in Cohort 2 will be treated prior to patients being treated in Cohort 3. Patients will be dosed approximately every 12 hours with food to help ensure consistent plasma levels are achieved, except for Visit 6 (Week 4, Day 7) when blood for fasting pharmacokinetic (PK) analysis will be drawn prior to the morning dose.

- Cohort 1: 20 mg/kg/day divided twice daily (BID) for 4 weeks.
- Cohort 2: Titration period of 20 mg/kg/day divided BID for 5 days, followed by 30 mg/kg/day divided BID for 4 weeks.
- Cohort 3: 10 mg/kg/day divided twice daily (BID) for 4 weeks.

Eligible patients will be provided with their titration dose during their Baseline Visit (5 days at 20 mg/kg/day for Cohorts 2).

During the Treatment Period, patients will be dosed for 4 weeks during which the investigator will assess tolerability and effect. Patients will return to the site at the end of Week 2 (Visit 4) to evaluate medical status (seizure diary, vital signs, and neurological exam), clinical laboratory assessments, and assess AEs.

At Visit 5 (Week 4, Day 6), the patient will have a repeat 4-hour video-EEG including hyperventilation to count the number of absence seizures captured, and blood for PK analysis will be drawn. Blood for PK analyses will be drawn at Visit 3, Visit 5 (fed; Week 4, Day 6) and Visit 6 (fasted; Week 4, Day 7), or the Early Withdrawal Visit. The investigator will assess tolerability and efficacy.

Following the completion of the Treatment Period (Visit 6), patients will have the option to continue treatment in an open-label long-term safety study. Patients who choose to enroll in the long-term safety study will not have a follow-up phone call. Patients who do not choose to enroll in the long-term safety study will taper the dose of Cannabidiol Oral Solution according to the following schedule: doses between 20-30 mg/kg/day will be reduced to 20 mg/kg/day

for five days and then discontinued; doses ≤ 20 mg/kg/day can be discontinued without titration. This can be modified by the investigator based upon the patient's response. Patients will receive a follow-up phone call 14 days after completing Visit 6 (End of Study).

Available safety data will be reviewed on an ongoing basis to ensure doses are generally well tolerated. Details of the safety data review will be provided in the Data Monitoring Charter.

Follow-Up Period

A follow-up phone call will occur 14 days after Visit 6 (End of Study) of the study to assess AEs, AEDs, and record concomitant medications.

Study Assessments

Safety assessments for all patients will include medical history, physical examination, vital signs (seated blood pressure, pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, and urinalysis), 12-lead ECG, prior medication history (assessment of past/current AEDs and concomitant medications), C-SSRS, and AE assessments.

A complete physical examination will be done at Screening (Visit 1). A neurological examination (complete at Screening [Visit 1] and brief at all other study visits) and vital signs will be assessed at Screening (Visit 1), Baseline (Visit 2), Treatment Period (Visits 3 [Week 1], 4 [Week 2], and 6 [Week 4, End of Study]), or at the Early Withdrawal Visit. Visit 6 is the End of Study visit for patients who complete the study.

Clinical laboratory blood tests (hematology, chemistry) will be obtained during the Screening (Visit 1), Treatment Period (Visits 3, 4, and 6 [End of Study]) or at the Early Withdrawal Visit. Urinalysis will be obtained during Screening (Visit 1) and at Visit 6 (End of Study) or the Early Withdrawal Visit. Concomitant AED blood levels will be determined at Baseline (Visit 2), Visit 6 (End of Study), or the Early Withdrawal Visit.

A 12-lead electrocardiogram (ECG), will be completed during Screening (Visit 1), Treatment Period (Visit 6 [End of Study]) or at the Early Withdrawal Visit.

For patients aged 7 to 17 years and if the developmental level is appropriate, the Columbia-Suicide Severity Rating Scale [(C-SSRS) Children's or Adult's version as appropriate based on age] will be utilized to assess suicidality at the following study visits: Screening (Visit 1) and Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit. For patients who are less than 7 years of age or for whom the C-SSRS is inappropriate due to the patient's developmental functioning, a clinical assessment will be made.

All adverse events (AEs) that arise during the Screening, Titration, Treatment, and Follow-up Periods will be documented. Concomitant medications will be reviewed and documented at each visit. A meal diary will be completed at Baseline (Visit 2), and for 24 hours before each PK sampling visit at Visit 3 and Visit 5 (Week 4, Day 6).

To assess PK parameters, blood draws will be obtained at Visit 3, Visit 5 (fed; Week 4, Day 6) and Visit 6 (fasted; Week 4, Day 7), or the Early Withdrawal Visit. Blood draws for PK values at Visits 5 and 6 will occur as follows:

Fasting/Fed	PK Sample Visits	Time points
Fed: Patients should arrive without food and the morning dose. Site provides a high fat/high calorie food then doses patient	Visit 5 (Week 4, Day 6)	Pre-dose (before meal/morning dose) and 2, 4, 6 hours after the morning dose (but before next dose)
Fasted (2 hours before dose until 2 hours after dose): Patients should arrive without food and the morning dose. Site provides a standard meal 2 hours after dose.	Visit 6 (Week 4, Day 7)	Pre-dose and 2 (before meal), 4, 6 hours after the morning dose (but before next dose)

To assess efficacy, a 4-hour video-EEG including hyperventilation will be obtained at the Baseline Visit (Visit 2), Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit. Absence seizures will be counted by an electrophysiologist not involved with the study. Further details will be provided in the video-EEG Charter.

Daily seizure diaries will be completed throughout the Titration and Treatment Periods, or the Early Withdrawal Visit. The daily record will ask: "How many absence seizures did the patient have today?".

To assess efficacy, the Clinical Global Impression – Global Improvement (CGI-I) assessment will be completed by the investigator at Visit 3, Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit.

Number of patients (planned):

Approximately 30 patients (10/cohort), 3 to 12 years of age (inclusive) at time of onset, who are 3-17 years of age (inclusive) at time of consent, who have treatment-resistant childhood absence seizures will be enrolled in the study.

Diagnosis and main criteria for inclusion:

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

Inclusion criteria

1. Patient and/or parent(s)/caregiver(s) fully comprehend the informed consent form (ICF) and assent form, understand all study procedures, and can communicate satisfactorily with the investigator and study coordinator, in accordance with applicable laws, regulations, and local requirements.
2. Male or female between 3 and 12 years (inclusive) at the time of onset and between 3 and 17 years of age (inclusive) at the time of consent.

3. Body weight ≥ 10 kg.
4. Diagnosed with childhood absence epilepsy (CAE), confirmed by EEG with at least 3 bursts of general spike wave (GSW of 2.7 to 5 hertz lasting ≥ 3 seconds) during the 4-hour EEG, and has had an adequate trial of at least two (2) AEDs and are treatment-resistant to at least one AED.
5. Willingness to not start a ketogenic diet during the Baseline or Treatment Period.
6. A female patient is eligible to participate in the study if she is:
   a. Premenarchal, or
   b. Of childbearing potential with a negative urine pregnancy test at the Screening Visit. If sexually active, she must agree to fulfill one of the following requirements:
      i. Complete abstinence from intercourse for 24 weeks prior to administration of the first dose of the investigational product, throughout the Treatment Period, and 2 weeks after completion or premature discontinuation from the investigational product, and agreement to use a double barrier method if she becomes sexually active.
      ii. Use of acceptable methods of contraception throughout the study and 2 weeks after completion or premature discontinuation from investigational product. The acceptable method of contraception is double barrier method (i.e., condom plus spermicide or a condom plus intrauterine device [IUD], diaphragm, or stable hormonal contraceptive use for at least 3 months before screening and through 28 days after study completion).
7. A sexually active male patient or partner of an enrolled subject must be willing to use acceptable methods of contraception throughout the study and for 2 weeks after completion of study participation or discontinuation from investigational product. The acceptable methods of birth control are abstinence or double barrier birth control (i.e., condom plus spermicide or a condom plus one of the methods listed in [7]).
8. In the opinion of the investigator, the parent(s)/caregiver(s) is willing and able to comply with the study procedures and visit schedules, including venipuncture, and the Follow-up Visits.
9. 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 (hematology, chemistry, and urinalysis) completed during the Screening Visit that would prohibit the patient from safely participating in the trial as judged by the investigator.

Exclusion criteria

1. Patient or parent(s)/caregiver(s) have daily commitments during the study duration that would interfere with attending all study visits.
2. Has a history of active nonfebrile seizures other than absence seizures (e.g., tonic, atonic, or myoclonic seizures). History of any other seizure type currently in remission must be adjudicated by the medical monitor.

3. Has a history of febrile seizures after 3 years of age.
4. Has a history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy.
5. Currently taking felbamate
6. Currently taking phenytoin, fluvoxamine, carbamazepine, or St. John's Wort.
7. Currently taking concomitant medications that are strong inhibitors/inducers/sensitive substrates with a narrow therapeutic index for cytochrome P450 3A4 (CYP3A4), CYP2C9, or CYP2C19 [Note: Stable doses of Valproic Acid during the screening, titration, treatment, and follow-up periods are permitted].
8. Currently on a ketogenic diet.
9. In the opinion of the investigator, any clinically significant, unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems.
10. Clinically significant abnormal liver function test (LFT) values, including:
    a. Albumin, direct bilirubin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN).
11. History or presence of abnormal ECGs that are clinically significant in the opinion of the investigator.
12. Has a current or history of clinically significant intellectual disability or major psychiatric disease, including autism spectrum disorder, which would interfere with compliance.
13. For patients aged 7 to 17 years of age and for whom the C-SSRS is developmentally appropriate, an affirmative answer to queries regarding active suicidal ideation with some intent to act but without a specific plan or active suicidal ideation with a specific plan and intent on the C-SSRS assessment at the Screening Visit. Patients who have significant findings for suicidal ideation as assessed by the C-SSRS must be referred to the investigator for follow-up evaluation.
14. Any history of attempted suicide.
15. Previously received any investigational drug or device or investigational therapy within 30 days before Screening.
16. Taken any cannabinoids (cannabidiol, Δ^9-tetrahydrocannabinol [Δ^9-THC], hemp oil, Realm Oil, or marijuana) in the 30 days prior to the Screening Visit.
17. History of an allergic reaction or a known or suspected sensitivity to any substance that is contained in the investigational product formulation.
18. Known infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
19. In the opinion of the investigator, the patient is unsuitable in any other way to participate in this study.
20. Body weight < 10 kg or > 90 kg.

Investigational product, dosage and mode of administration:

Cannabidiol Oral Solution: an oral solution containing pharmaceutical grade cannabidiol (pharmaceutical grade, synthetic).

The investigational product will be dosed orally in three dose cohorts. Total daily doses of 10, 20, or 30 mg/kg/day will be administered in two daily doses of 5, 10, or 15 mg/kg/dose. Doses higher than 20 mg/kg/day will be titrated. Cannabidiol Oral Solution will be administered with food except for when fasting PK values will be obtained (Visit 6 [Week 4, Day 7]).

Duration of treatment:

The maximum duration of the study from screening to the follow-up of AEs call will be approximately 10 weeks.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Efficacy Endpoints

- % change in absence seizure counts comparing treatment at Week 4 (Visit 5) video-EEG to Baseline (Visit 2) video-EEG and comparing doses.
- % change in time to absence seizure during hyperventilation testing on video-EEG comparing treatment at Week 4 (Visit 5) to Baseline (Visit 2) and comparing doses.
- % patients seizure free at Week 4 (Visit 5) based on seizure diary, comparing doses.
- Investigator CGI-I at Week 4 (Visit 5) comparing doses.

Safety Endpoints

- Incidence, type, and severity of AEs and serious adverse events (SAEs) occurring during the Treatment Period (i.e., treatment-emergent adverse events [TEAEs]).
- Incidence, type, timing, and severity of AEs and serious adverse events (SAEs) occurring during the Safety Period. (i.e., treatment-emergent adverse events [TEAEs]).
- Changes from Baseline (Visit 2) in vital signs during the Treatment Period.
- Changes from Screening (Visit 1) in laboratory values (hematology, chemistry, and urinalysis) during the Treatment Period.

Pharmacokinetic Endpoints

- C_{max} and dose-normalized C_{max}: fed (Visit 5 [Week 4, Day 6]) and fasted (Visit 6 [Week 4, Day 7]).

- Area under the plasma concentration curve ($AUC_{(0-t)}$) and dose normalized area under the curve ($AUC_{(0-t)}$ /Dose): fed (Visit 5 [Week 4, Day 6]) and fasted (Visit 6 [Week 4, Day 7]).
- Trough plasma concentration (C_{trough}) and dose normalized trough plasma concentration (C_{trough}/Dose): fed (Visit 5 [Week 4, Day 6]), and fasted (Visit 6 [Week 4, Day 7), Visit 3, or the Early Withdrawal Visit.

Statistical Methods:

Efficacy Analysis

The results of the video-EEG (including presence or absence of hyperventilation), CGI-I, and seizure diary assessments will be summarized using summary tables, listings, and figures (TLFs), as appropriate. Continuous variables will be summarized using descriptive statistics: sample size (n), mean, standard deviation (SD), or coefficient of variation (CV %) as appropriate, median, interquartile range, minimum and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

Safety Analysis

All safety assessments, including AEs, clinical laboratory evaluations, vital signs, 12-lead ECGs, C-SSRS (children and adolescents aged 7 to 17 years, if appropriate), concomitant AED blood levels, physical and neurological examinations will be listed. When appropriate, they will be summarized with descriptive statistics by age and dose cohort. 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, which will be summarized for each treatment group.

Clinical laboratory findings and vital signs will be summarized for all patients for observed values and change from baseline. Shifts from baseline according to normal range criteria will also be presented for all patients.

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 Analysis

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

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

Missing Data

There will be no imputation of the missing values for the efficacy, safety, or PK population. All assessments will be conducted based on all the observed data.

Table 1: Schedule of Events

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

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

[a] Screening should occur within 28 (± 5) days.

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

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

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

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

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

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

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

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

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

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

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

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

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

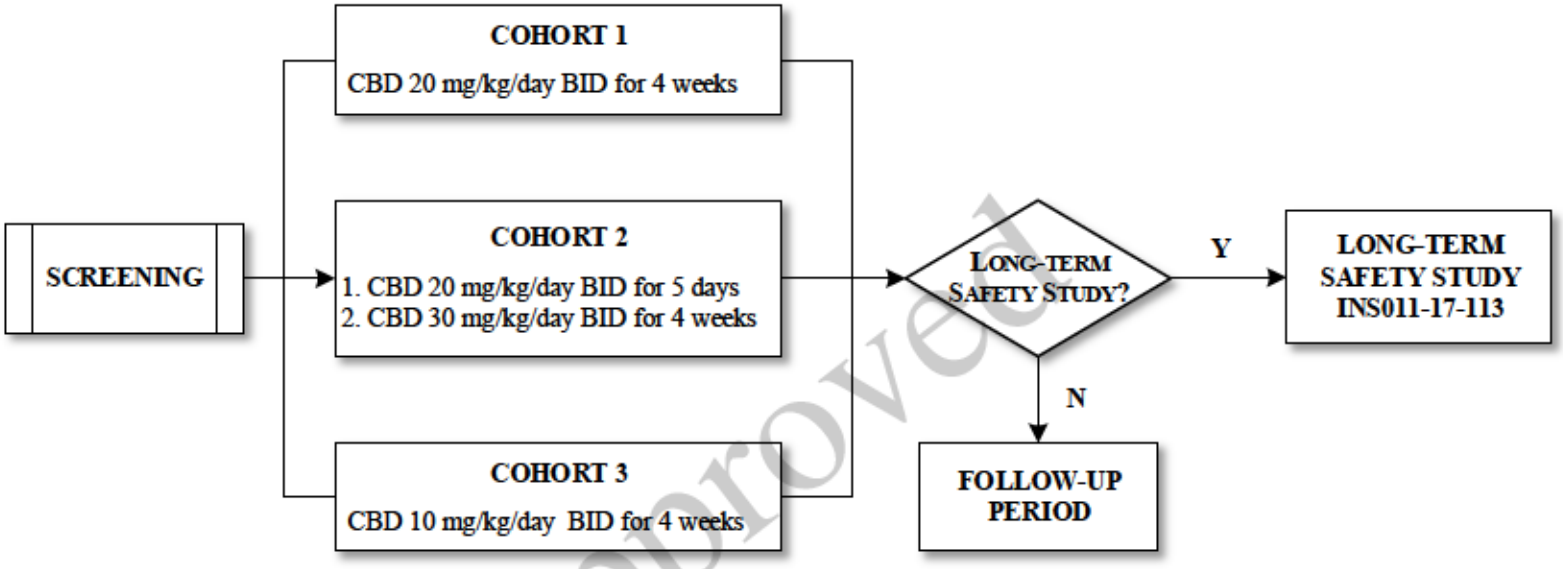
[o] Study drug will be collected but not dispensed.

[p] If the patient withdraws prematurely from the Treatment Period, all Early Withdrawal procedures should be conducted. Site staff will follow up with the patient at 14 days after completion of the Early Withdrawal Visit via the telephone to collect information regarding AEs, AEDs, and concomitant medications.

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

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

Figure 1: Study Design Schematic



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

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

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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
AEDs	anti-epileptic drugs
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the concentration-time curve from 0 (predose) to the last quantifiable concentration
BMI	body mass index
BID	bis in die (twice a day)
BUN	blood urea nitrogen
CAE	childhood absence epilepsy1A1
CB1	cannabinoid receptor 1
CB2	cannabinoid receptor 2
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression – Global Improvement
cGMP	current Good Manufacturing Practices
CLB	clobazam
C_{max}	maximum plasma concentration
C_{trough}	plasma trough concentrations
CNS	central nervous system
CRF	case report form
CRA	clinical research associate
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	coefficient of variation

Abbreviation or Specialist Term	Explanation
CYP	cytochrome P450
CYP1A1	Cytochrome P450 1A1
CYP2C19	Cytochrome P450 2C19
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytochrome P450 3A4
CYP3A5	Cytochrome P450 3A5
DEA	Drug Enforcement Administration
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
EENT	eyes, ears, nose, and throat
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICD	informed consent document
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL-2	interleukin-2
IP	Investigational product
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MCT	medium chain triglycerides
MedDRA	Medical Dictionary for Regulatory Activities
OH	hydroxy
PK	pharmacokinetic(s)
pKa	acid dissociation constant
PT	preferred term
SAE	serious adverse event

Abbreviation or Specialist Term	Explanation
SAP	Statistical Analysis Plan
SOP	standard operating procedure
t½	elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
Δ^9-THC	Δ^9-tetrahydrocannabinol
THC	tetrahydrocannabinol
US	United States

1. INTRODUCTION

Data presented in this section includes 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 synthetic pharmaceutical grade 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 nonpsychoactive and the second most abundant cannabinoid. It has demonstrated a potential benefit to treating subjects 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 Insys' 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 $\geq$ 99.5% pure[6] and can be consistently produced without 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 hepatic microsomal metabolism through 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]

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 with cytochrome P450 (CYP) proteins.[15] Its interactions with human drug metabolizing enzymes (as a substrate, inhibitor, or inducer) were recently reviewed.[16,17]

Cannabidiol is metabolized primarily in the liver by CYP3A4 and to a lesser extent by CYP2C19. Specifically, CBD inhibits CYP3A4, CYP3A5, and CYP1A1 in vitro.[18,19,20] It also appears to inhibit CYP2C9[21] and the transport protein P-glycoprotein.[22,23]

Further details may be found in the Investigator's Brochure (IB).[1]

1.2. Nonclinical Experience

1.2.1. Safety

In a nonclinical setting, single-dose toxicology studies of CBD reveal a relatively safe toxicology profile except at very high doses of the drug substance. Repeated dose toxicology studies highlight a potential impact of CBD on spermatogenesis, follicle-stimulating hormone levels, and a subset of immune responses. Full detail of these results may be found in the IB.[1]

1.2.2. Efficacy in Animal Models of Epilepsy

Plant-derived CBD studies show antiepileptic,[24] antipsychotic, anti-dystonic, anti-emetic, and anti-inflammatory properties in animal models.[25] These models support exploring the use of CBD for the treatment of epilepsy.[26]

The anticonvulsant activity of oral CBD was investigated in adult rat model of seizures (induced by maximal electroshock or audiogenic sources).[27] 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 CBD was drug specific.

1.3. Clinical Experience

A Phase 1/2 study to assess the pharmacokinetics (PK) and safety of multiple doses (10 mg/kg/day, 20 mg/kg/day, and 40 mg/kg/day) of pharmaceutical grade, synthetic Cannabidiol Oral Solution in 61 pediatric subjects with treatment-resistant seizure disorders aged 1 year to 17 years has been completed by the Sponsor (Protocol INS011-14-029). Subjects were exposed for a period of approximately 11 days before qualifying to participate in the long-term extension study (INS011-14-030). Analyses demonstrated that:

- Cannabidiol levels on Day 10 appeared to increase proportionally with weight-based dose across the dosing cohorts, notwithstanding the two different formulations of the investigational product.
- 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 area under the concentration-time curve in plasma during a dosing interval ($AUC_{(0\text{-}tau)}$) 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.
- Geometric mean maximum plasma concentrations (C_{max}) of cannabidiol at steady-state were 91.0 (Cohort 1 [10 mg/kg/day]), 126.0 (Cohort 2 [20 mg/kg/day]), and 314.5 ng/mL (Cohort 3 [40 mg/kg/day]) for all age categories combined.
- Median time to maximum plasma concentration of cannabidiol at steady-state ranged from 2.0 to 3.0 hours for all age categories combined.

- Geometric means of cannabidiol apparent terminal half-life ($t_{1/2}$) ranged from 19.5 to 29.6 hours following a single dose of Cannabidiol Oral Solution for all age categories combined.
- Accumulation in cannabidiol exposures was approximately 3- to 4-fold for all age categories combined. Dosing cohort total geometric means ranged from 2.6 to 3.1 for accumulation ratio for C_{max} and from 3.6 to 4.4 for accumulation ratio for $AUC_{(0\text{-}tau)}$.
- Most of the dosing cohort total variability in cannabidiol exposures after repeated dosing (Day 10) was lower than Day 1. Single and repeated administrations of Cannabidiol Oral Solution resulted in highly variable systemic exposures of cannabidiol.
- There were no apparent formulation-related differences observed in terms of $t_{1/2}$, dose-normalized exposures, and variability.
- There were no clear trends for age-related differences in cannabidiol exposures, but exposure in infants tended to be lower than that in children and adolescents, approximately half at the highest dose (40 mg/kg/day).
- Approximately 50% of subjects enrolled were receiving clobazam. Clobazam and cannabidiol have a reciprocal drug-drug interaction leading to the increased mean exposures of both cannabidiol (approximately 2.5-fold), and clobazam as well as norclobazam (approximately 3-fold) at the highest dose (40 mg/kg/day).
- No apparent gender differences were observed for cannabidiol pharmacokinetics (PK).
- Pharmacokinetic results for 7-hydroxy cannabidiol and its statistical evaluations generally reflected those observed for parent cannabidiol.
- There were no quantifiable levels Δ^9-THC and 11-hydroxy-Δ^9-THC measured following cannabidiol dosing.
- All doses of the investigational product were generally well-tolerated, although dose-titration was not employed. Dose-dependent adverse events (AEs) that occurred in multiple dosing cohorts and increased as the dose of the investigational product increased included diarrhea, flatulence, weight increase, somnolence, and psychomotor hyperactivity. Events of somnolence were potentially also related to concomitant use of clobazam with the investigational product, but this was not formally investigated in this study.
- There were no clinically relevant differences in the AE profile among subjects in the infant, child, and adolescent age categories.
- Serious adverse events were reported rarely and were consistent with underlying disease or procedures.
- Although this was not designed as an efficacy study, parent(s)/caregiver(s) and investigators both reported notable reductions in severity of mental illness (Clinical Global Impression of Severity) and improvement in global subject status (Clinical Global Impression of Improvement).

- The average change in weekly seizure rates (seizures of all types) was variable across subjects, dosing cohorts, and over time. Although the mean change in the weekly rate tonic seizures at the end of the study compared with baseline generally decreased in a potentially dose-dependent manner, no pattern was observed for the other types of seizures reported. It was thought that tonic seizures were most representative of seizure control in this study.

In addition, a long-term safety study (Protocol INS011-14-030) for subjects enrolled in the PK study above was recently completed. Fifty-two of 61 subjects from INS011-14-029 enrolled; 45 subjects completed the study. There were seven early termination subjects (two for withdrawal of consent, two for AEs of aggressions and sleepiness/irritability, one for the SAE of worsening seizures, one for lack of efficacy, and one subject with a genetic mutation died from systemic sepsis and multi-organ failure considered nonrelated). Overall, 91% of the subjects were taking doses greater than 20mg/kg/day, with 38% of subjects tolerating 40mg/kg/day. The most common drug-related AEs reported were anemia (5 subjects), somnolence (4 subjects), and weight increased (4 subjects). However, the weight increases ranged from a little over 2 lbs to approximately 7 lbs.

During the study, trough PK values were drawn and interim PK data for CBD and 7-OH CBD from Visit 5 (Week 4) to Visit 8 (Week 24) were analyzed. Dose-normalized mean trough CBD concentrations ranged from 11.9 to 16 (ng/mL)/(mg/kg), showing relatively stable levels for up to 6 months dosing Cannabidiol Oral Solution at various dose levels. After one month of dosing, there did not appear to be much accumulation, even though early accumulation had likely happened when compared with INS011-14-029 results. High variability in trough CBD concentrations was observed, but the extent of variability between visits was similar as reported in the previous 029 study.

An open-label study of Cannabidiol Oral Solution (20 mg/kg/day and 40 mg/kg/day) in pediatric subjects with infantile spasms refractory to ACTH and vigabatrin recently was halted due to futility (Protocol INS011-15-054) because only one out of nine patients achieved a complete response.

A food effect study of Cannabidiol Oral Solution in normal healthy adults (Protocol INS011-15-043) recently completed and the results are presented in the IB. Analysis demonstrated significantly higher CBD levels when administered with food.

INS011-16-093 evaluated the effect of food on the bioavailability of multiple test formulations of Cannabidiol Oral Solution: MCT Oil formulation (100 mg/mL), Sesame Seed Oil formulation (100 mg/ml), and alcohol-containing formulation (80 mg/mL). The Sesame Oil formulation was studied both after subjects were fed a high fat diet and after a fast; the other formulations were tested after a high-fat diet. CBD C_{max} was approximately 12.3-fold higher after administration of food compared to fasting. Comparing the Sesame Oil fasting levels to the fed formulations there was a 12.7-fold higher CBD C_{max} (MCT formulation) and 11.2-fold higher C_{max} (alcohol-containing formulation).

Clinical data described in the following sections were collected following administration of various extracts of CBD as oral solutions or solid formulations.

1.3.1. Pharmacokinetics

Study INS011-14-029 is a Phase 1/2 study assessing the PK and safety of multiple doses of CBD. In this recently completed PK trial using synthetic CBD (Cannabidiol Oral Solution, Insys Development Company, Inc.), each cohort consisted of 20 pediatric subjects from 1 to 17 years of age who received 10 mg/kg/day, 20 mg/kg/day, or 40 mg/kg/day over a period of 10 days. Subjects were dosed as in-subjects for Day 1 through Day 8. Subjects were then offered the opportunity to be discharged on Day 8 with readmission on Day 10 and a final study visit on Day 11. Cohort 1 received a formulation containing alcohol; Cohorts 2 and 3 received the final alcohol-free formulation containing medium chain triglycerides (MCT) oil. It was designed to have three age groups consisting of infants (1-2 yrs: 5 subjects), children (2 to <12 yrs: 9 subjects), and adolescents (12 to <17 yrs: 6 subjects) in each cohort.

Single oral administration of CBD at 5, 10, 20 mg/kg per dose resulted in mean peak levels of about 59, 111, and 232 ng/mL, respectively, and terminal half-life value of about 17 to 29 hours. The PK of CBD in different age groups was comparable at each dose level. Steady-state seemed to be achieved within 2 to 4 days after daily dose of 10, 20, 40 mg/kg/day CBD, with typical steady-state peak levels of about 120, 214, and 427 ng/mL, respectively, and a terminal half-life of 4 to 9 hours on Day 10.

Dose proportional increase in CBD exposures on Day 10 was clearly observed in mean $C_{max,ss}$ and AUC_{tau} even if two different formulations were used in the study. Accumulation after repeated doses was about 2-fold. Plasma levels of 7-hydoxy (7-OH) CBD were generally similar to the parent drug.

Cannabidiol and clobazam (CLB) appear to have a drug-drug interaction based on the observed plasma levels of both drugs: Increase in mean exposures of clobazam on Day 10 by cannabidiol was shown in a dose-dependent matter (×1.2, × 1.5, × 2.6 of clobazam for 10, 20, 40 mg/kg/day CBD, respectively). Similarly, mean N-desmethyl CLB plasma levels following 20 or 40 mg/kg/day of CBD were increased by CBD.

However, there were appreciable changes in cannabidiol exposures on Day 10 only at the highest CBD dose (40 mg/kg/day), but not in the lower doses, with co-administration of clobazam.

The food effect study (Protocol INS011-15-043) demonstrates a 15 to 18-fold and 85-fold higher AUC and C_{max}, respectively, in the fed state versus the fasting state after single administration of 20 mg/kg Cannabidiol Oral Solution (300 mg/mL) in healthy adults. Inter-subject variability was dramatically reduced with food: 55%CV from 125% for C_{max} and 35%CV from 78% for AUC_{0-inf}. Median time to maximum cannabidiol exposure (T_{max}) occurred approximately 6 hours earlier under fed conditions compared to that after fasted conditions (6.00 h Fed vs. 12.00 h Fasted). The highest exposures with food in terms of AUC and C_{max} were 24040 h·ng/mL and 4190 ng/mL, respectively.

INS011-16-093 evaluated the effect of food on the bioavailability of multiple test formulations of Cannabidiol Oral Solution: MCT Oil formulation (100 mg/mL), Sesame Seed Oil formulation (100 mg/ml), and alcohol-containing formulation (80 mg/mL). The Sesame Oil formulation was studied both after subjects were fed a high fat diet and after a fast; the other formulations were tested after a high-fat diet. CBD C_{max} was approximately 12.3-fold higher after administration of food compared to fasting. Comparing the Sesame Oil fasting levels to the fed formulations there

was a 12.7-fold higher CBD C_{max} (MCT formulation) and 11.2-fold higher C_{max} (alcohol-containing formulation).

As a comparison, mean peak and total exposures in all age groups (Protocol INS011-14-029) on Day 10 were within 16 to 36% to dose-adjusted exposures in fed adults (Protocol INS011-14-029).

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.[28] 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.[17] recently reviewed the safety of CBD in humans examined in 221 subjects 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.[2,29] 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. Furthermore, between 300 and 1500 mg have been used in humans without toxicity or SAEs.[30,31,32]

1.3.3. Clinical Safety Data

The following specific examples detail selected studies of the safety of CBD use in humans:

- Daily dosing of 10 mg/kg CBD was evaluated in a study of 15 subjects diagnosed with Huntington's disease.[30] Only 15 abnormal clinical laboratory values were associated with CBD treatment; these were largely limited to 4 subjects and exhibited no obvious pattern. No significant or clinical differences in CBD were observed in a cannabis-specific side-effect inventory.
- Chronic oral administration of 10 mg CBD daily for 21 days does not induce any changes in neurological (including electroencephalogram [EEG]), clinical (including electrocardiogram [ECG]), psychiatric, blood, or urine examinations in both healthy volunteers and epileptic subjects.[2]
- Oral administration of CBD in healthy volunteers (3 mg/kg daily for 30 days) and in epileptic subjects (200 to 300 mg daily for 135 days) was well tolerated. No signs of toxicity or serious side-effects were detected on neurological and physical examinations, blood and urine analysis, ECG, or EEG.[2,29]
- Administration of single and repeated doses of CBD for up to 20 days at a dose of 1200 mg/day does not impact pulse rate and blood pressure in human subjects with previous experience to cannabis smoking.[34]
- Three subjects with treatment-resistant schizophrenia have been dosed with 40 to 1280 mg/day of CBD for up to 4 weeks without reporting side-effects.[35]
- Two subjects diagnosed with bipolar affective disorder did not report adverse effects upon receiving 600 to 1200 mg/day of CBD for up to 24 days.[36]

- In addition, a long-term safety study (Protocol INS011-14-030) for subjects enrolled in the PK study above recently completed. Fifty-two of 61 subjects from INS011-14-029 enrolled; 45 subjects completed the study. There were seven early termination subjects (two for withdrawal of consent, two for AEs of aggressions and sleepiness/irritability, one for the SAE of worsening seizures, one for lack of efficacy, and one subject with a genetic mutation died from systemic sepsis and multi-organ failure considered nonrelated). Overall, 91% of the subjects were taking doses greater than 20mg/kg/day, with 38% of subjects tolerating 40mg/kg/day. The most common drug-related AEs reported were anemia (5 subjects), somnolence (4 subjects), and weight increased (4 subjects). However, the weight increases ranged from a little over 2 lbs to approximately 7 lbs.

1.3.4. Efficacy in Human Epilepsy

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

Plant-derived CBD was examined as an adjunctive therapy in 15 subjects with secondary generalized epilepsy with temporal focus who were refractory to conventional treatment.[2,3] The eight subjects randomized to the active arm received 200 to 300 mg/day of CBD or placebo for up to 4.5 months in addition to previously established antiepileptic drugs (AEDs).[2,29] Subjects tolerated CBD well, with no signs of toxicity or serious side-effects. Four of the eight subjects receiving CBD remained almost free of convulsive crises throughout the study and three others experienced partial improvement. The clinical condition of seven subjects receiving placebo remained unchanged and one subject improved.

Parents of children with treatment-resistant epilepsy have sought CBD-enriched cannabis for treatment.[4] In a survey, these parents reported dosages of CBD ranging from <0.5 to 28.6 mg/kg/day, as per results from medical cannabis testing facilities. Sixteen (84%) of the 19 parents eligible to respond to the survey reported a reduction in their child's seizure frequency while taking CBD-enriched cannabis. Of these, 2 (11%) reported complete seizure-freedom, 8 (42%) reported >80% reduction in seizure frequency, and 6 (32%) reported a 25% to 60% seizure reduction. Reported side-effects included fatigue and somnolence.

Realm Oil is an extract from a strain of cannabis known as Charlotte's Web and contains a CBD:Δ^9-THC ratio >20:1. Gedde and Maa[5] reported on a small group of pediatric subjects diagnosed with various types of epilepsy who took Realm Oil for ≥3 months. Baseline seizure frequency for these subjects ranged from 5 to 2800 events per week. Eight (8, 73%) of these subjects reported a 95% to 100% reduction in seizure occurrence, 1 (9%) reported 75% reduction, and 2 (18%) reported 20% to 45% reduction.

1.4. Childhood Absence Epilepsy

Although there are currently two drugs approved for childhood absence epilepsy (CAE), valproate and ethosuximide, neither are ideal. Valproate has potentially serious side effects, including weight gain, polycystic ovary disease, liver failure, and significant teratogenic effects. Ethosuximide does not control general tonic-clonic seizures that can co-exist with CAE. In a recent study comparing ethosuximide, valproic acid, and lamotrigine, freedom from failure rates where treatment failure was defined as persistence of absence seizures at Week 16 or 20, a

generalized tonic-clonic seizure at any time, excessive drug-related systemic toxicity, dose-limiting toxicity after a single downward dose modification, or withdrawal initiated by the parent or physician, was 53% (ethosuximide), 58% (valproic acid), and 29% (lamotrigine).[37] Therefore, there is still an unmet need for more effective anti-epileptic drugs with less side effects for these seizures. As CBD has been demonstrated to be effective in the treatment of cortical mediated epileptic encephalopathies[38], Insys is proposing a multiple-site, open-label, dose-finding proof of concept study of Cannabidiol Oral Solution for the treatment of refractory childhood absence epilepsy. Children have many absence seizures a day, and seizures may be provoked by hyperventilation during EEG, a 4-hour video-EEG including hyperventilation will be utilized as a biomarker in this proof of concept study. In addition, a seizure diary will be collected.

1.5. Dose Selection Rationale

Doses up to 40 mg/kg/day were given in the Phase 1/2 PK study (Protocol INS011-14-029) and the long-term safety study (Protocol INS011-14-030). The maximum dose given was 3200 mg/day in an adolescent. These doses were generally well tolerated even without titration. Only six subjects required a decrease in dose due to somnolence (2), abdominal pain (1), diarrhea (1), irritability (1), and seizure (1).

An interim safety report was generated for the long-term safety study (INS011-14-030) with a data cut off-of 31 Jan 2017. As of the data cut off, 52 patients (9 infants, 26 children, and 17 adolescents) were enrolled and had received at least one dose of the investigational product in this study. As of the data cut-off, the mean modal dose (defined as the dose with the longest duration) for all patients was 23.47 mg/kg/day, and the mean number of days on-study for all patients was 220.6 (Table 2). Overall, seven patients (13.5%) had dose reductions resulting from an AE, and 3 patients (5.8%) had dose reductions due to other reasons (Table 3). The frequency of dose reductions was greater in the patients receiving 40 mg/kg/day compared with patients receiving 10 mg/kg/day (seven patients [35.0%] and two patients [14.3%], respectively). Overall, one patient (1.9%) was taking <10 mg/kg/day, 10 patients (19.2%) were taking between 10 and <20 mg/kg/day, 20 patients (38.5%) were taking between 20 and <40 mg/kg/day, and 20 patients (38.5%) were taking 40 mg/kg/day as of the data cut-off (Table 4). Therefore, this study will evaluate the doses of 20 mg/kg/day, 30 mg/kg/day and 10 mg/kg/day. Doses higher than 20 mg/kg/day will be titrated.

Table 2: Cannabidiol Oral Solution Exposure (Study INS011-14-030)

	Infants (N=9)	Children (N=26)	Adolescents (N=17)	All Patients (N=52)
Modal Dose (mg/kg/day)[a]				
n	9	26	17	52
Mean (SD)	31.11 (10.541)	21.17 (12.719)	22.94 (12.127)	23.47 (12.488)
Median	40.00	20.00	20.00	20.00
Min, Max	20.0, 40.0	0.5, 40.0	10.0, 40.0	0.5, 40.0
Total Duration of Study Drug at Any Dose (Days)				
n	9	26	17	52
Mean (SD)	234.1 (91.73)	210.0 (118.73)	229.7 (95.47)	220.6 (105.86)
Median	253.0	249.0	250.0	250.5
Min, Max	1, 336	1, 344	1, 336	1, 344

Abbreviations: BID = twice daily; Max = maximum; Min = minimum; N = total number; n = sample size; SD = standard deviation.
[a] For each patient, the modal dose corresponds to the dose with the longest duration.
Duration = Date of last dose – date of first Dose + 1.
The study drug is Cannabidiol Oral Solution (300 mg/mL) administered BID
Age Category: Infants = 1 to <2 years of age, Children = 2 to <12 years of age, Adolescents = 12 to ≤17 years of age. Age categories are based on the patient's age at the beginning of their previous study (INS011-14-029).
Source: Interim Safety Report for Study INS011-14-030.

Table 3: Cannabidiol Oral Solution Dose Reduction by Initial Planned Dose (Study INS011-14-030)

	10 mg/kg/day (N=14)	20 mg/kg/day (N=18)	40 mg/kg/day (N=20)	All Patients (N=52)
Number of patients with ≥1 dose reductions	2 (14.3%)	0	7 (35.0%)	9 (17.3%)
Reason for dose reductions				
Adverse event	1 (7.1%)	0	6 (30.0%)	7 (13.5%)
Lack of efficacy	0	0	0	0
PK analysis result	0	0	0	0
Other	1 (7.1%)	0	2 (10.0%)	3 (5.8%)

The study drug is Cannabidiol Oral Solution (300 mg/mL) administered BID
Patients having more than 1 dose reduction due to the same reason are counted only once for this reason.
Patients may be included in more than 1 reason for dose reduction.
Source: Interim Safety Report for Study INS011-14-030.

Table 4: Distribution of Patients by Cannabidiol Oral Solution Dose (Study INS011-14-030)

	Infants (N=9)	Children (N=26)	Adolescents (N=17)	All Patients (N=52)
Number of patients taking dose as of cut-off				
<10 mg/kg/day	0	1 (3.8%)	0	1 (1.9%)
10 -<20 mg/kg/day	0	7 (26.9%)	3 (17.6%)	10 (19.2%)
20 -<40 mg/kg/day	3 (33.3%)	9 (34.6%)	8 (47.1%)	20 (38.5%)
≥40 mg/kg/day	6 (66.7%)	8 (30.8%)	6 (35.3%)	20 (38.5%)

The study drug is Cannabidiol Oral Solution (300 mg/mL) administered BID
Age Category: Infants = 1 to <2 years of age, Children = 2 to <12 years of age, Adolescents = 12 to ≤17 years of age. Age categories are based on the patient's age at the beginning of their previous study (INS011-14-029).
Source: Interim Safety Report for Study INS011-14-030.

1.6. Summary of Potential Risks and Benefits

As reviewed in Section 1.2 and Section 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 2 isozymes, as well as having small effects on CYP3A5, CYP1A1, and CYP2C9.
- 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.[39]

The inclusion/exclusion criteria, concomitant medication guidelines, and safety monitoring (AEs, clinical laboratory, vital signs, ECG, 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 patient participation should a safety issue arise (see Section 3.3).

Two facets of the current treatment landscape for pediatric patients with treatment-resistant absence seizures support the potential benefit for subjects in this study. First, pediatric patients with treatment-resistant absence seizures continue to experience a significant unmet medical need despite ongoing treatment with currently available medications and procedures. Patients included in this study may potentially benefit from treatment with Cannabidiol Oral Solution. Devinsky et al.[40] recently noted that pediatric subjects with treatment-resistant seizures are particularly good candidates for CBD intervention. Data reviewed in Section 1.2.2 and Section 1.3.4 demonstrate that CBD has shown preliminary efficacy in treating epilepsy in several early-stage nonclinical and clinical studies, respectively. This study is expected to serve as a critical step in the development of Cannabidiol Oral Solution as a treatment for refractory childhood absence epilepsy.

Second, synthetic pharmaceutical grade 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 assess the efficacy of Cannabidiol Oral Solution in the treatment of pediatric patients with treatment-resistant childhood absence seizures.

2.2. Secondary Objectives

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

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2, open-label, dose-finding study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of three doses (20, 30, and 10 mg/kg/day) of Cannabidiol Oral Solution. Doses exceeding 30 mg/kg/day will not be examined in this study. The study design and patient progression through the study is outlined in Figure 1.

Study participants will be pediatric patients age 3 to 17 (inclusive) experiencing treatment-resistant childhood absence seizures who satisfy all inclusion/exclusion criteria. The study will consist of a Screening Period, a Titration Period, a Treatment Period, and a Follow-up Period. A total of 30 patients will be enrolled in the study. Ten patients will be enrolled in each of the three dose cohorts, and no patient will participate in more than one cohort.

Each patient will complete a Screening Period for up to 28 (± 5) days. Eligible patients will have a baseline 4-hour video-EEG that will include hyperventilation. The investigator may use results of a previously obtained EEG to guide selection of the appropriate patients but the Baseline Visit video-EEG will be used for determination of eligibility and will be evaluated by an electrophysiologist not involved in the study. Details of the video-EEG assessment will be provided in the video-EEG Charter.

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

3.1.1. Titration and Treatment Periods

Thirty patients in total will be enrolled into one of three dose cohorts; ten patients per cohort. Patients in Cohort 1 will be treated before patients are treated in Cohort 2, and patients in Cohort 2 will be treated prior to patients being treated in Cohort 3. Patients will be dosed approximately every 12 hours with food to help ensure consistent plasma levels are achieved, except for Visit 6 (Week 4, Day 7) when blood for fasting pharmacokinetic (PK) analysis will be drawn prior to the morning dose.

- Cohort 1: 20 mg/kg/day divided twice daily (BID) for 4 weeks.
- Cohort 2: Titration period of 20 mg/kg/day divided BID for 5 days, followed by 30 mg/kg/day divided BID for 4 weeks.
- Cohort 3: 10 mg/kg/day divided twice daily (BID) for 4 weeks. Eligible patients will be provided with their titration dose during their Baseline Visit (5 days at 20 mg/kg/day for Cohorts 2).

During the Treatment Period, patients will be dosed for 4 weeks during which the investigator will assess tolerability and effect. Patients will return to the site at the end of Week 2 (Visit 4) to evaluate medical status (seizure diary, vital signs, and neurological exam), clinical laboratory assessments, and assess AEs.

At Visit 5 (Week 4, Day 6), the patient will have a repeat 4-hour video-EEG including hyperventilation to count the number of absence seizures captured, and blood for PK analysis

will be drawn. Blood for PK analyses will be drawn at Visit 3, Visit 5 (fed; Week 4, Day 6) and Visit 6 (fasted; Week 4, Day 7), or the Early Withdrawal Visit. The investigator will assess tolerability and efficacy.

Following the completion of the Treatment Period (Visit 6), patients will have the option to continue treatment in an open-label long-term safety study. Patients who choose to enroll in the long-term safety study will not have a follow-up phone call. Patients who do not choose to enroll in the long-term safety study will taper the dose of Cannabidiol Oral Solution according to the following schedule: doses between 20-30 mg/kg/day will be reduced to 20 mg/kg/day for five days and then discontinued; doses ≤ 20 mg/kg/day can be discontinued without titration. This can be modified by the investigator based upon the patient's response. Patients will receive a follow-up phone call 14 days after completing Visit 6 (End of Study).

Available safety data will be reviewed on an ongoing basis to ensure doses are generally well tolerated. Details of the safety data review will be provided in the Data Monitoring Charter.

3.1.2. Follow-Up Period

A follow-up phone call will occur 14 days after Visit 6 (End of Study) of the study drug to assess AEs, AEDs, and record concomitant medications.

3.1.3. Study Assessments

Safety assessments for all patients will include medical history, physical examination, vital signs (seated blood pressure, pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, and urinalysis), 12-lead ECG, prior medication history (assessments of past/current AEDs and concomitant medications), C-SSRS, and AE assessments.

A complete physical examination will be done at Screening (Visit 1). A neurological examination (complete at Screening [Visit 1] and brief at all other study visits) and vital signs will be assessed at Screening (Visit 1), Baseline (Visit 2), Treatment Period (Visits 3 [Week 1], 4 [Week 2], and 6 [Week 4, End of Study]), or at the Early Withdrawal Visit. Visit 6 is the End of Study visit for patients who complete the study.

Clinical laboratory blood tests (hematology, chemistry) will be obtained during the Screening (Visit 1), Treatment Period (Visits 3, 4, and 6 [End of Study]) or at the Early Withdrawal Visit. Urinalysis will be obtained during Screening (Visit 1), and at Visit 6 (End of Study) or at the Early Withdrawal Visit. Concomitant AED blood levels will be determined at Baseline (Visit 2), Visit 6 (End of Study), or the Early Withdrawal Visit.

A 12-lead electrocardiogram (ECG), will be completed during Screening (Visit 1), Treatment Period (Visit 6 [End of Study]) or at the Early Withdrawal Visit.

For patients aged 7 to 17 years and if the developmental level is appropriate, the Columbia-Suicide Severity Rating Scale [(C-SSRS) Children's or Adult's version as appropriate based on age] will be utilized to assess suicidality at the following study visits: Screening (Visit 1) and Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit. For patients who are less than 7 years of age or for whom the C-SSRS is inappropriate due to the patient's developmental functioning, a clinical assessment will be made.

All adverse events (AEs) that arise during the Screening, Titration, Treatment, and Follow-up Periods will be documented. Concomitant medications will be reviewed and documented at each visit. A meal diary will be completed at Baseline (Visit 2), and for 24 hours before each PK sampling visit at Visit 3 and Visit 5 (Week 4, Day 6), or the Early Withdrawal Visit.

To assess PK parameters, blood draws will be obtained at Visit 3, Visit 5 (fed; Week 4, Day 6) and Visit 6 (fasted; Week 4, Day 7), or the Early Withdrawal Visit. Blood draws for PK values at Visits 5 and 6 will occur as follows:

Fasting/Fed	**PK Sample Visits**	**Time points**
Fed: Patients should arrive without food and the morning dose. Site provides a high fat/high calorie food then doses patient	Visit 5 (Week 4, Day 6)	Pre-dose (before meal/morning dose) and 2, 4, 6 hours after the morning dose (but before next dose)
Fasted (2 hours before dose until 2 hours after dose): Patients should arrive without food and the morning dose. Site provides a standard meal 2 hours after dose.	Visit 6 (Week 4, Day 7)	Pre-dose and 2 (before meal), 4, 6 hours after the morning dose (but before next dose)

To assess efficacy, a 4-hour video-EEG including hyperventilation will be obtained at the Baseline Visit (Visit 2), Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit. Absence seizures will be counted by an electrophysiologist not involved with the study. Further details will be provided in the video-EEG Charter.

Daily seizure diaries will be completed throughout the Titration and Treatment Periods, or the Early Withdrawal Visit. The daily record will ask: "How many absence seizures did the patient have today?".

To assess efficacy, the Clinical Global Impression – Global Improvement (CGI-I) assessment will be completed by the investigator at Visit 3, Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit. All screening, efficacy, and safety assessments will be performed according to the schedule of assessments summarized in Table 1.

3.2. Patient Selection

3.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria

1. Patient and/or parent(s)/caregiver(s) fully comprehend the informed consent form (ICF) and assent form, understand all study procedures, and can communicate satisfactorily with the investigator and study coordinator, in accordance with applicable laws, regulations, and local requirements.
2. Male or female between 3 and 12 years (inclusive) at the time of onset and between 3 and 17 years of age (inclusive) at the time of consent.
3. Body weight ≥ 10 kg.
4. Diagnosed with childhood absence epilepsy (CAE), confirmed by EEG with at least 3 bursts of general spike wave (GSW of 2.7 to 5 hertz lasting ≥ 3 seconds) during the 4-hour EEG, and has had an adequate trial of at least 2 AEDs and are treatment-resistant to at least one AED.
5. Willingness to not start a ketogenic diet during the Baseline or Treatment Period.
6. A female patient is eligible to participate in the study if she is:
   a. Premenarchal, or
   b. Of childbearing potential with a negative urine pregnancy test at the Screening Visit. If sexually active, she must agree to fulfill one of the following requirements:
      i. Complete abstinence from intercourse for 24 weeks prior to administration of the first dose of the investigational product, throughout the Treatment Period, and 2 weeks after completion or premature discontinuation from the investigational product, and agreement to use a double barrier method if she becomes sexually active.
      ii. Use of acceptable methods of contraception throughout the study and 2 weeks after completion or premature discontinuation from investigational product. The acceptable method of contraception is double barrier method (i.e., condom plus spermicide or a condom plus intrauterine device [IUD], diaphragm, or stable hormonal contraceptive use for at least 3 months before screening and through 28 days after study completion).
7. A sexually active male patient or partner of an enrolled subject must be willing to use acceptable methods of contraception throughout the study and for 2 weeks after completion of study participation or discontinuation from investigational product. The acceptable methods of birth control are abstinence or double barrier birth control (i.e., condom plus spermicide or a condom plus one of the methods listed in [7]).
8. In the opinion of the investigator, the parent(s)/caregiver(s) is willing and able to comply with the study procedures and visit schedules, including venipuncture, and the Follow-up Visits.

9. 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 (hematology, chemistry, and urinalysis) completed during the Screening Visit that would prohibit the patient from safely participating in the trial as judged by the investigator.

3.2.2. Exclusion Criteria

1. Patient or parent(s)/caregiver(s) have daily commitments during the study duration that would interfere with attending all study visits.
2. Has a history of active nonfebrile seizures other than absence seizures (e.g., tonic, atonic, or myoclonic seizures). History of any other seizure type currently in remission must be adjudicated by the medical monitor.
3. Has a history of febrile seizures after 3 years of age.
4. Has a history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy.
5. Currently taking felbamate
6. Currently taking phenytoin, fluvoxamine, carbamazepine, or St. John's Wort.
7. Currently taking concomitant medications that are strong inhibitors/inducers/sensitive substrates with a narrow therapeutic index for cytochrome P450 3A4 (CYP3A4), CYP2C9, or CYP2C19 [Note: Stable doses of Valproic Acid during the screening, titration, treatment, and follow-up periods are permitted].
8. Currently on a ketogenic diet.
9. In the opinion of the investigator, any clinically significant, unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems.
10. Clinically significant abnormal liver function test (LFT) values, including:

    a. Albumin, direct bilirubin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN).
11. History or presence of abnormal ECGs that are clinically significant in the opinion of the investigator.
12. Has a current or history of clinically significant intellectual disability or major psychiatric disease, including autism spectrum disorder, which would interfere with compliance.
13. For patients aged 7 to 17 years of age and for whom the C-SSRS is developmentally appropriate, an affirmative answer to queries regarding active suicidal ideation with some intent to act but without a specific plan or active suicidal ideation with a specific plan and intent on the C-SSRS assessment at the Screening Visit. Patients who have significant findings for suicidal ideation as assessed by the C-SSRS must be referred to the investigator for follow-up evaluation.
14. Any history of attempted suicide.

15. Previously received any investigational drug or device or investigational therapy within 30 days before Screening.
16. Taken any cannabinoids (cannabidiol, Δ^9-tetrahydrocannabinol [Δ^9-THC], hemp oil, Realm Oil, or marijuana) in the 30 days prior to the Screening Visit.
17. History of an allergic reaction or a known or suspected sensitivity to any substance that is contained in the investigational product formulation.
18. Known infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV).
19. In the opinion of the investigator, the patient is unsuitable in any other way to participate in this study.
20. Body weight < 10 kg or > 90 kg.

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). Furthermore, 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.
- Patient does not tolerate 10 mg/kg/day.
- Sponsor decides to stop the study.

In the event of a patient's withdrawal, the investigator will promptly notify the sponsor. Every effort will be made to complete the end-of-study assessments.

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.

3.4. Dose Adjustment Criteria

Doses will not be adjusted in this study.

3.5. Stopping Rules

The investigator reserves the right to terminate the study in the interests 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 from the study if they meet the following criteria:

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

For patients meeting the above criteria, the investigator will arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, bilirubin, and alkaline phosphatase (ALP), detailed history, and physical examination. Patients will be followed until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state. If the patient is unable to return to the investigational site, repeat assessments may be performed at a local laboratory.

4. TREATMENTS

4.1. Treatments Administered

In the Treatment Period, Cannabidiol Oral Solution will be dosed orally in three dose cohorts. Patients or parent/caregiver will be instructed how to measure, take their dose, and record their dose in the dosing diary when the IP is dispensed for the first time.

Total daily doses of 10, 20, or 30 mg/kg/day will be administered with food in two daily doses of 5, 10, or 15 mg/kg/dose approximately every 12 hours. Patients in Cohort 1 will be treated prior to initiation of enrollment into Cohort 2, and patients in Cohort 2 will be treated prior to initiation of enrollment into Cohort 3. Doses higher than 20 mg/kg/day will be titrated as described in Section 4.4. Cannabidiol Oral Solution will be administered within 30 minutes after a meal, except during Visit 6 when fasting PK values will be obtained.

4.2. Identity of Investigational Product

The active pharmaceutical ingredient (API) in Cannabidiol Oral Solution is a pharmaceutical grade synthetic CBD 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-brown colored solution (CBD concentration of 100 mg/mL) filled into a 30 mL amber glass vial. More detailed information may be found in the IB.[1]

4.3. Method of Assigning Subjects to Treatment Groups

Eligible patients will be sequentially assigned to each dose cohort. That is, the first 10 eligible patients will be in Cohort 1, and so on.

4.4. Selection and Timing of Dose for Each Subject

Ten patients will be enrolled in each of three dose cohorts:

- Cohort 1: 20 mg/kg/day divided BID for 4 weeks.
- Cohort 2: 20 mg/kg/day divided BID for 5 days followed by 30 mg/kg/day divided BID for 4 weeks.
- Cohort 3: 10 mg/kg/day divided BID for 4 weeks.

Subjects will take each dose approximately every 12 hours with food in order to ensure consistent plasma levels are achieved, except for Visit 6 when blood for fasting pharmacokinetic analysis will be drawn prior to the morning dose. The date and time of all investigational product administrations will be documented in the case report form (CRF) from the seizure diary.

4.5. Blinding and Unblinding Treatment Assignment

Not applicable.

4.6. Treatment Compliance

The prescribed dosage, timing, and mode of administration of IP may not be changed unless there is a protocol-specified up titration or a safety concern or toxicity is identified for a patient.

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 used and 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 used and unused supplies of the investigational product may be destroyed via the use of a third-party vendor or be returned to the Sponsor or a designee after the final drug accountability check has been performed. 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).

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 administered at the investigator's discretion.

4.7.2. Prohibited Therapies

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

- Any cannabinoids besides the study drug (cannabidiol, Δ^9-THC, hemp oil, Realm Oil or marijuana).
- Phenytoin, fluvoxamine, carbamazepine, or St. John's Wort.
- Medications that are strong inhibitors/inducers/sensitive substrates with a narrow therapeutic index for CYP3A4, CYP2C9, or CYP2C19 [Note: Stable doses of Valproic Acid during the screening, titration, treatment, and follow-up periods are permitted].
- Any other investigational drug or investigational device.
- Introduction of new anti-epileptic drugs (AEDs) or therapies (VNS, ketogenic diet) during the study is prohibited during the Treatment Period, but allowed during the Safety Period.

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.

4.8. Treatment After the End of Study

A final follow-up phone call will be conducted 14 days after completion of Visit 6 (End of Study).

5. STUDY DRUG MATERIALS AND MANAGEMENT

5.1. Labeling and Packaging

5.1.1. Labeling

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

5.1.2. Packaging

The investigational product will be supplied in 30 mL containers of a 100 mg/mL strength (i.e., 3000 mg per container).

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

Please refer to the Cannabidiol Oral Solution IB[1] for additional information on the drug formulation.

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, storage conditions, and expiry date. 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.

5.2. Dispensing and Storage

IP will be stored at controlled room temperature (20 to 25 degrees Celsius, 68 to 77 degrees Fahrenheit) at the study centers.

Cannabis and its constituents (including CBD) are Schedule I controlled substances 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.

The DEA regulations detail specific security requirements for storage of the investigational product. 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 one 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.

Doses of IP will be administered from the Schedule I-licensed study center.

The study centers are required to provide complete information, including case report forms (CRFs) and final outcomes, on all instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in 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 subjects dropped out of the study.

5.3. Drug Supply and 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 Cannabidiol Oral Solution 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 may be destroyed by via the use of a third-party vendor or be returned to the Sponsor or a designee after the final drug accountability check has been performed. 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).

6. STUDY ASSESSMENTS

6.1. Efficacy Assessments

6.1.1. Video-Electroencephalography (Video-EEG)

A 4-hour video-EEG will be performed for all subjects at Baseline (Visit 2), Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit. Hyperventilation will be conducted during the video-EEG. As overt clinical signs may or may not be present during the GSW bursts, response testing during the GSW bursts is encouraged, if possible, but not required.

Details regarding requirements for conducting the video-EEG and the independent central reader's review and assessment of the video-EEG is outlined in the EEG Charter.

6.1.2. Clinical Global Impression – Global Improvement (CGI-I)

The CGI-I will be assessed by the investigator at Visit 3, Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit.

6.1.3. Seizure Diaries

Seizure diaries will be dispensed during the Screening Visit (Visit 1) to collect daily seizure activity throughout the Screening, Titration, and Treatment Periods, or the Early Withdrawal Visit. Each day, the patient or parent/caregiver will respond to the question: "How many absence seizures did the patient have today?"

6.2. Safety Assessments

Safety assessments for all patients will include medical history, physical examination, vital signs (seated blood pressure, pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, and urinalysis), 12-lead ECG, concomitant AED blood levels, prior medication history (assessments of past/current AEDs and concomitant medications), C-SSRS, and AE assessments.

6.2.1. Demographics and Medical History

Each potential study participant will have the following assessments performed by the investigator or designee during the Screening Period (Days -28 to -1): demographic data, including sex, date of birth, race, ethnicity, medical/surgical history, estimate of historic seizure count from patient or parent, record of past and current AEDs, and concomitant medications.

6.2.2. Physical Examinations

A physical examination will be conducted for every patient during the Screening Visit (Visit 1). The examination will include evaluation of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities. Height and weight will be measured during Visits 1, 3, 6 (End of Study) or the Early Withdrawal Visit.

6.2.3. Neurological Examinations

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

6.2.4. Vital Signs

Vital signs (seated blood pressure, pulse rate, temperature and respiration rate) will be measured during Screening (Visit 1), Baseline Visit (Visit 2), Treatment Period (Visits 3, 4, and 6 [End of Study]) or the Early Withdrawal Visit.

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

6.2.5. Electrocardiograms

A resting 12-lead ECG will be conducted for every patient during Screening (Visit 1), Treatment Period (Visit 6 [End of Study]) or the Early Withdrawal Visit.

6.2.6. Clinical Laboratory Assessments

Blood samples for hematology and chemistry assessments will be collected during Screening (Visit 1), Treatment Period (Visits 3, 4, and 6 [End of Study]) or the Early Withdrawal Visit. Urine samples for urinalysis will be collected during Screening (Visit 1), Treatment Period (Visit 6 [End of Study]) or the Early Withdrawal Visit.

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC), and platelet count.
- Chemistry: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na^+), potassium (K^+), chloride (Cl^-), lactate dehydrogenase (LDH), uric acid, glucose, and calcium.
- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range a microscopic examination will be performed.

Concomitant AED blood levels will be determined at Baseline (Visit 2), Visit 6 (End of Study), or the Early Withdrawal Visit.

6.2.7. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a prospective assessment tool routinely used in studies of drugs with any potential for CNS effects. It captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. For patients aged 7 to 17 years and if the developmental level is appropriate, the questionnaire will be completed at Screening (Visit 1) and Visit 5 (Week 4, Day 6) or the Early Withdrawal Visit. For patients who are less than 7 years or for whom the C-SSRS is inappropriate due to the patient's developmental functioning, a

clinical assessment will be made following FDA guidelines. (https://www.fda.gov/downloads/drugs/guidances/ucm225130.pdf).

6.2.8. Adverse Events and Serious Adverse Events

6.2.8.1. 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 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 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.

Absence seizures will not be considered AEs. However, new seizure types and injury resulting from a seizure will be captured as AEs.

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.

Previous clinical trial experience has shown that somnolence, diarrhea, and transaminase elevations may be associated with CBD treatment. Therefore, Insys Development Company has identified these as Adverse Events of Special Interest.

6.2.8.2. 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.

Action taken will be categorized as none, study drug discontinued, dose modified, required concomitant medication, required procedure, or other.

Event outcome at resolution or time of last follow-up will recorded as event resolved, resolved with sequelae, ongoing, or death.

6.2.8.3. 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.
- 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.
- 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.
- 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.

6.2.8.4. 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.

6.2.8.5. Serious Adverse Events Actions Taken

Actions taken may consist of:

- None: No action taken
- Treatment: Standard of care measures instituted
- Drug withdrawn: Study medication was permanently discontinued because of the AE
- Unknown: Not known, not observed, not recorded, or refused

6.2.8.6. Serious Adverse Events 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

6.2.8.7. 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 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 Insys within 24 hours of the investigators first knowledge of the event.

Sponsor contact information is listed below:

PPD

Director of Pharmacovigilance
Insys Development Company, Inc.
Email: clinicalpv@insysrx.com

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.

6.2.8.8. 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.

6.2.8.9. Safety Data Review

Available safety data will be reviewed on an ongoing basis to ensure doses are generally well tolerated. Details of the safety data review will be provided in the Data Monitoring Charter.

6.2.8.10. Special Considerations

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 subjects who are taking concomitant medications that are metabolized by CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP1A2, or by P-glycoprotein with special care.

6.2.9. Pharmacokinetics Assessments

To assess PK parameters, blood draws will be obtained at Visit 3, Visit 5 (fed; Week 4, Day 6) and Visit 6 (fasted; Week 4, Day 7), or the Early Withdrawal Visit. Blood draws for PK values at Visits 5 and 6 will occur as follows:

Fasting/Fed	PK Sample Visits	Time points
Fed: Patients should arrive without food and the morning dose. Site provides a high fat/high calorie food then doses patient	Visit 5 (Week 4, Day 6)	Pre-dose (before meal/morning dose) and 2, 4, 6 hours after the morning dose (but before next dose)
Fasted (2 hours before dose until 2 hours after dose): Patients should arrive without food and the morning dose. Site provides a standard meal 2 hours after dose.	Visit 6 (Week 4, Day 7)	Pre-dose and 2 (before meal), 4, 6 hours after the morning dose (but before next dose)

Whole blood will be obtained in a Vacutainer® tube containing K_2EDTA. Specific sample collection instructions will be provided in a separate pharmacokinetic manual.

7. STUDY PROCEDURES

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

7.1. Screening

Potential study subjects will be examined before the start of the study to determine their eligibility for participation. Informed consent must be obtained and signed before initiation of screening activities. The following screening procedures and assessments must be performed within 28 (+/- 5) days before the day of enrollment in the study:

- Obtain written informed consent/assent (if appropriate).
- Review of inclusion and exclusion criteria.
- Review of historic seizure counts based on patient and caregiver reports.
- Dispense seizure and meal diary.
- Record demographics.
- Assessment of past/current AEDs and other concomitant medications.
- Record medical/surgical history.
- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate), including height and weight.
- Collect blood samples (clinical chemistry and hematology).
- Perform 12-lead ECG.
- Collect urine sample for urinalysis.
- Urine dipstick pregnancy test (all female subjects of childbearing potential).
- Perform a complete physical examination.
- Perform a complete neurological examination.
- Measure and record height and weight.
- Complete C-SSRS.
- Review AEs.

7.2. Titration Period

7.2.1. Baseline (Visit 2, Day 1)

The following procedures and assessments will be performed at the Visit 2:

- Review of inclusion and exclusion criteria.
- 4-hour video-EEG.
- Review and record seizure and meal diary.

- Dispense meal diary.
- Assessment of past/current AEDs and concomitant medications.
- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Concomitant AED levels.
- Perform a brief neurological examination.
- If patient is in Cohort 2, dispense study drug for the Titration Period after eligibility is confirmed, and train patient/caregiver to administer and record treatments.
- Review AEs.

During the 5-day (for Cohort 2) Titration Period, the seizure diary should be completed daily. The meal diary should be completed for 24 hours prior to Visit 3. The investigator or designee will call or e-mail daily and record past/current AEDs, concomitant medications, and AEs.

7.3. Treatment Period

7.3.1. Visit 3 (Day 1)

The following procedures and assessments will be performed on Day 1:

- Review and record seizure diary and meal diary.
- Assessment of past/current AEDs and other concomitant medications.
- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Collect blood samples (clinical chemistry and hematology, and PK sample)
- Perform a brief neurological examination.
- Record height and weight.
- Collect, review, and dispense Cannabidiol Oral Solution. If patient is in Cohort 1 (20 mg/kg/day) or Cohort 3 (10 mg/kg/day), train patient/caregiver to administer and record treatments.
- Dispense seizure diary.
- Investigator complete CGI-I.
- Review AEs.

7.3.2. Visit 4 (Week 2)

The following procedures and assessments will be performed:

- Review and record seizure diary.
- Assessment of past/current AEDs and other concomitant medications.

- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Collect blood samples (clinical chemistry and hematology).
- Perform a brief neurological examination.
- Review AEs.
- Collect, review, and dispense Cannabidiol Oral Solution.
- Dispense meal and seizure diary.

7.3.3. Visit 5 (Week 4, Day 6)

The patient should complete their meal diary for 24 hours prior to Visit 5, bring their morning dose of the IP with them to the study site and should not eat breakfast. The following procedures and assessments will be performed:

- Review and record seizure and meal diaries.
- 4-hour video-EEG.
- Assessment of past/current AEDs and other concomitant medications.
- PK blood draws will be taken pre-dose, 2, 4, and 6 hours after the morning dose (but before the next dose). The pre-dose blood sample should be collected BEFORE dosing with "high-fat" breakfast (dose will be administered within 30 minutes of start of breakfast).
- Dosing with Cannabidiol Oral Solution.
- Investigator complete CGI-I.
- Complete C-SSRS
- Review AEs.

7.3.4. End of Study: Visit 6 (Week 4, Day 7)

The patient should bring their morning dose of medications with them to the study site and should not eat for at least two hours prior to arrival. The following procedures and assessments will be performed:

- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Draw blood for clinical laboratory tests (clinical chemistry and hematology) and concomitant AED level.
- PK blood draws will be taken pre-dose, 2, 4, and 6 hours after the morning dose (but before the next dose). Patient will be fasted for 2 hours before dose. A standard breakfast will be provided 2 hours after the dose, AFTER the 2-hour blood draw.
- Dosing with Cannabidiol Oral Solution (patient should not eat until two hours after dose and the 2-hour PK blood is drawn).

- Collect urine sample for urinalysis.
- Perform 12-lead ECG.
- Perform a brief neurological examination.
- Record height and weight.
- Review AEs.

7.4. Early Withdrawal Visit

The patient should complete their seizure diary for 7 days prior to the visit, complete their meal diary for 24 hours prior to the visit, and bring their morning dose of the medications with them to the study. The following procedures and assessments will be performed at Visit 7 or following patient withdrawal:

- 4-hour video-EEG.
- Review and collect seizure and meal diaries.
- Review and collect meal diary.
- Assessment of past/current AEDs and other concomitant medications.
- Concomitant AED levels.
- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Collect blood samples (clinical chemistry and hematology).
- 12-lead ECG.
- PK blood sample.
- Collect urine sample for urinalysis.
- Perform a brief neurological examination.
- Record height and weight.
- Investigator complete CGI-I.
- Complete C-SSRS.
- Review/Collect Cannabidiol Oral Solution.
- Review AEs.

7.5. Visit 7 (Follow-Up Period)

For patients who do not choose to enroll in the long-term safety study, the following assessments will be performed by phone call at 14 days after completion of Visit 6 (End of Study):

- Record past/current AEDs and other concomitant medications.
- Review AEs.

8. STATISTICS

8.1. Efficacy Endpoints

- % change in absence seizure counts comparing treatment at Week 4 (Visit 5) video-EEG to Baseline (Visit 2) video-EEG and comparing doses.
- % change in time to absence seizure during hyperventilation testing on video-EEG comparing treatment at Week 4 (Visit 5) to Baseline (Visit 2) and comparing doses.
- % patients seizure free at Week 4 (Visit 5) based on seizure diary, comparing doses.
- Investigator CGI-I at Week 4 (Visit 5) comparing doses.

8.2. Safety Endpoints

Changes in safety endpoints will be reported as mean/median change from baseline at relevant time points and as a listing of events that fall outside normal limits.

- Incidence, type, and severity of AEs and serious adverse events (SAEs) occurring during the Treatment Period (i.e., treatment-emergent AEs [TEAEs]).
- Changes from Baseline (Visit 2) in vital signs during the Treatment Period.
- Changes from Screening in laboratory values (hematology, chemistry, and urinalysis) during the Treatment Period.

8.3. Pharmacokinetic Endpoints

- C_{max} and dose-normalized C_{max}: fed (Visit 5 [Week 4, Day 6]) and fasted (Visit 6 [Week 4, Day 7]).
- Area under the plasma concentration curve ($AUC_{(0-t)}$) and dose normalized area under the curve ($AUC_{(0-t)}$/Dose): fed (Visit 5 [Week 4, Day 6]) and fasted (Visit 6 [Week 4, Day 7]).
- Trough plasma concentration (C_{trough}) and dose normalized trough plasma concentration (C_{trough}/Dose): fed (Visit 5 [Week 4, Day 6]) and fasted (Visit 6 [Week 4, Day 7], Visit 3, or the Early Withdrawal Visit.

8.4. Sample Size Determination

Due to the exploratory nature of the study, the sample size is not based on formal statistical considerations. The sample size is based on experience from similar studies to obtain adequate preliminary efficacy, safety, and tolerability data to achieve the objectives of the study.

8.5. Analysis Populations

Statistical analysis will be conducted on all enrolled subjects.

8.6. Statistical Analyses

This section presents a summary of the planned statistical analyses. A Statistical Analysis Plan (SAP) that describes the details of the analyses to be conducted will be finalized prior to database lock.

Summary statistics will be provided for the variables described as follows. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation, median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

8.6.1. Study Subjects and Demographics

8.6.1.1. Disposition and Withdrawals

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

8.6.1.2. Protocol Deviations

Protocol deviations will be identified and classified as minor or major.

8.6.1.3. Demographics and Other Baseline Characteristics

These analyses will be conducted for the safety populations.

Demographic and baseline characteristics (including age, gender, race, weight, height, and BMI) will be summarized by treatment group and for the overall population by descriptive statistics. No formal statistical analyses will be performed. Medical history, clinical laboratory test results, and ECG assessments will be listed and summarized by descriptive statistics.

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

8.6.2. Exposure and Compliance

The exposure to study medication will be summarized by descriptive statistics. Any compliance deviations will be listed.

8.6.3. Efficacy Analyses

The results of the video-EEG (including presence or absence of hyperventilation), CGI-I, and seizure diary assessments will be summarized using summary tables, listings, and figures (TLFs), as appropriate. Continuous variables will be summarized using descriptive statistics: sample size (n), mean, standard deviation (SD), or coefficient of variation (CV %) as appropriate, median, interquartile range, minimum and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

8.6.4. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the safety population. No formal inferential analyses will be conducted for safety variables. Data listings will be provided for protocol-specified safety data.

8.6.4.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA, version 20.0 or higher) will be used to classify all AEs. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

The number and percentage of subjects with AEs will be displayed for each treatment group by system organ class and preferred term. Summaries of AEs by severity and relationship to the IP will also be provided. Serious AEs (SAEs) and AEs resulting in discontinuation will be summarized separately in a similar manner. Patient listings of AEs and SAEs will be produced.

8.6.4.2. Clinical Laboratory Evaluations

For the continuous hematology and chemistry laboratory parameters, descriptive statistics will be presented for values collected at Screening (Visit 1), Treatment Period (Visits 3, 4, and 6 [End of Study]) or the Early Withdrawal Visit, and for any clinically significant changes from Screening. For urinalysis, descriptive statistics will be presented for values collected at Screening (Visit 1), and at Visit 6 (End of Study) or the Early Withdrawal Visit, and for any clinically significant changes from Screening

8.6.4.3. Vital Signs

For blood pressure, pulse rate, temperature, and respiration rate, descriptive statistics will be presented for values collected at Screening (Visit 1), Baseline (Visit 2), Treatment Period (Visits 3, 4, and 6 [End of Study]) or the Early Withdrawal Visit, and for the changes from Baseline to Visit 6 (End of Study)/ Early Withdrawal.

8.6.4.4. Electrocardiograms

For the continuous ECG parameters, descriptive statistics will be presented for values collected at Screening (Visit 1), Visit 6 (End of Study) or the Early Withdrawal Visit, and for the changes from Screening (Visit 1) to Visit 6 (End of Study)/Early Withdrawal.

Additionally, the number and percentage of subjects will be presented as shift tables for the overall interpretation from Screening (normal or abnormal, not clinically significant [NCS]) to End of Study/Early Withdrawal (normal; abnormal, NCS; or abnormal, clinically significant [CS]).

8.6.4.5. Physical Examination Findings

Physical examination body systems will be presented as the number and percentage of subjects that have normal or abnormal results at Screening (Visit 1). The examination will include evaluation of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities.

8.6.4.6. Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS categorization based on Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories 1, 2, 3, 4, and 7 will be summarized as dichotomous endpoints at Screening (Visit 1), Treatment Period (Visit 5) or the Early Withdrawal Visit.

8.6.5. Interim Analysis

No interim analyses are planned.

8.6.6. Pharmacokinetic Analyses

Descriptive statistics of trough plasma concentration and PK parameters data for CBD and 7-OH CBD by Visit, Dose, and Response will be provided. The following noncompartmental PK parameters will be estimated from the plasma concentration-time data: area under the curve from time 0 to the last measured concentration (AUC_{0-t}) by maximum plasma concentration (C_{max}), and time to reach maximum plasma concentration (T_{max}) using Phoenix Winnonlin (Version 6.3 or higher; Pharsight Corporation, Cary, NC 27518, USA). Additional PK parameters may be estimated, as appropriate. Exploratory analysis of dose (exposure)-response relationship will be performed. Further population PK approach may be used for PK parameter estimation, as appropriate.

8.6.7. Missing Data

There will be no imputation of the missing values for the efficacy, safety, or PK population. All assessments will be conducted based on all the observed data.

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 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. 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 CRO 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 subjects 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 (ICF).
- 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.
- Study site personnel, including the investigator, have participated in a study initiation meeting.

9.3. Screen Failures

Subjects who screen fail may be re-screened for the study if deemed appropriate by the investigator and approved by the sponsor.

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 investigational product (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, the investigator agrees to maintain accurate CRFs/eCRFs and source documentation as part of the case histories for all subjects who sign an 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 central 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 subject's source data.

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

9.5. 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 subjects 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 subjects currently participating in the study complete all of the assessments for the Early Withdrawal Visit.

9.6. 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

9.6.1. Record Retention

The investigator shall retain and preserve one copy of all data generated during 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 has been approved or the sponsor has discontinued its research with the Investigational Product, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product

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

9.6.2. 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 subject.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor or its designee will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This trial will be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with the FDA CFR 312.50 and 312.56, and with the ICH guidelines on GCP (CPMP/ICH/135/95).

10.1. Changes To The Protocol

Only Insys may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the sponsor and the investigator. The only exception is when the investigator assesses a subject's safety will be compromised without immediate action. In these circumstances, immediate approval of the chairman of the IEC/IRB must be sought, and the investigator should inform the sponsor and the full IEC/IRB within 5 working days after the emergency occurred. All amendments that have an impact on patient risk or the study objectives, or require revision of the informed consent form, must receive approval from the IEC/IRB prior to their implementation.

10.2. Monitoring

The sponsor or sponsor's representative will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized sponsor/contract research organization (CRO) personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

10.3. Data Review Meeting

The sponsor will review all data reported in CRFs of all subjects before database lock. The data review meeting determines whether all enrolled subjects 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.

10.4. Protocol Violations

The investigator will conduct the study in compliance with the protocol approved by the IRB. Modifications to the protocol should not be performed without agreement of both the investigator and the sponsor. Changes to the protocol will require written IRB approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

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 subjects, the record should be immediately submitted to the sponsor, the CRO, and the IRB by the investigator and 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 CRO and written agreement of the sponsor.

When deviation from the protocol is required to eliminate immediate hazard(s) to subjects, the investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented in the CRF and source documentation.

10.5. 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.

11. REGULATORY AND ETHICAL CONSIDERATIONS

11.1. Regulatory Authority Approval

The investigator will ensure that the protocol and consent form 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 subjects, available safety information, information about payment and compensation available to subjects, 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.

11.2. 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 subjects 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.

11.3. 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.

11.4. Patient Informed Consent

The investigator or his/her designee will inform the patient of all aspects pertaining to their participation in the study. The process for obtaining patient 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 patient must both sign and date the informed consent document (ICD) before they can participate in the study. The patient 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 patient is entirely voluntary. The investigator or his/her designee must emphasize to the patient 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 IRB, and use of the amended form, including the necessity of re-consenting ongoing subjects.

11.5. 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.

12. DATA HANDLING AND RECORD KEEPING

The CRO will be responsible for data management and analysis. The procedures will be specified in the Data Management Plan.

12.1. 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 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.

12.2. Case Report Forms and Source Documents

The CRFs will be supplied by the CRO data management services. The complete CRFs will be reviewed, signed, and dated by the qualified investigator and a copy returned to the Sponsor with the final report.

Source documents are defined as original documents, data, and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media and/or x rays.

12.3. Documentation and Retention of Essential Documents

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 subject 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.

12.4. 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.

13. FACILITIES

Selection of specific study vendors is pending.

Clinical Laboratory:	Medpace 5375 Medpace Way Cincinnati, OH 45227
Bioanalytical Laboratory:	Worldwide Clinical Trials Early Phase Service/Bioanalytical Sciences, Inc. 8609 Cross Park Drive Austin, Texas 78754
Pharmacokinetic Analyses:	Worldwide Clinical Trials Early Phase Service/Bioanalytical Sciences, Inc. 8609 Cross Park Drive Austin, Texas 78754
Data Management:	PRA Health Sciences 4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612
Statistical Services:	PRA Health Sciences 4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612

14. USE OF INFORMATION AND PUBLICATION POLICY

14.1. 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 subjects enrolled in the study (by name and patient number). This list will be maintained at the site, and will not be retrieved by Insys.

14.2. 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.

15. REFERENCES (AVAILABLE UPON REQUEST)

1. Investigator's Brochure for Cannabidiol Oral Solution, Edition 6.0, 30 September 2016.
2. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacol*. 1980; 21: 175-185.
3. Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol*. 1981; 21: 417S-427S.
4. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav*. 2013; 29: 574-577.
5. Gedde MM, Maa E. Whole cannabis extract of high concentration cannabidiol may calm seizures in highly refractory pediatric epilepsies. *America Epilepsy Society Meeting* 2013; abstract: 3.300.
6. Sponsor's internal documentation of analysis.
7. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology* 1982; 76: 245-250.
8. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol*. 2001; 134: 845-852.
9. Kathmann M, Flau K, Redmer A, Trankle C, Schlicker E. Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors. *Naunyn Schmiedebergs Arch Pharmacol*. 2006; 372: 354-361.
10. Bornheim LM, Grillo MP. Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of cannabidiol-hydroxyquinone as a P450 inactivator. *Chem Res Toxicol*. 1998; 11: 1209 1216.
11. Ryan D, Drysdale AJ, Lafourcade C, Pertwee RG, Platt B. Cannabidiol targets mitochondria to regulate intracellular Ca2+ levels. *J Neurosci*. 2009; 29: 2053-2063.
12. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1A receptors. *Neurochem Res*. 2005; 30: 1037-1043.
13. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci US*. 2006; 103: 7895-7900.
14. Jones NA, Glyn SE, Akiyama S, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. *Seizure*. 2012; 21: 344-352.
15. Harvey DJ, Samara E, Mechoulam R. Comparative metabolism of cannabidiol in dog, rat and man. *Pharmacol Biochem Behav*. 1991; 40: 523-532.
16. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*. 2014 Feb; 46: 86-95.

17. Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side-effects of cannabidiol, a cannabis sativa constituent. *Curr Drug Saf.* 2011b; 6: 237-249.

18. Yamaori S, Ebisawa J, Okushima Y, Yamamoto I, Watanabe K. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety. *Life Sci.* 2011; 88: 730-736.

19. Yamaori S, Kushihara M, Yamamoto I, Watanabe K. Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. *Biochem Pharmacol.* 2010; 79: 1691-1698.

20. Johannessen SI, Landmark CJ. Antiepileptic drug interactions – principles and clinical implications. *Curr Neuropharmacol.* 2010; 8: 254-267.

21. Yamaori S, Koeda K, Kushihara M, Hada Y, Yamamoto I, Watanabe K. Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. *Drug Metab Pharmacokinet.* 2012; 27: 294-300.

22. Zhu HJ, Wang JS, Markowitz JS, et al. Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. *J Pharmacol Exp Ther.* 2006; 317: 850-857.

23. Holland ML, Panetta JA, Hoskins JM, Bebawy M, Roufogalis BD, Allen JD, et al. The effects of cannabinoids on P-glycoprotein transport and expression in multidrug resistant cells. *Biochem Pharmacol.* 2006; 71: 1146-1154.

24. Carlini EA, Cunha JM. Hypnotic and anti-epileptic effects of cannabidiol. *J Clin Pharmacol*. 1981; 21: 417S-427S.

25. Mechoulam R, Hanus L. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol.* 2002; 42: 11S-19S.

26. Massi P, Vaccani A, Ceruti S, Colombo A, Abbracchio MP, Parolaro D. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther*. 2004; 308: 838-845.

27. Consroe P, Wolkin A. Cannabidiol - antiepileptic drug comparisons and interactions in experimentally induced seizures in rats. *J Pharmacol Exp Ther*. 1977; 201: 26-32.

28. Zuardi AW, Morais SL, Guimarães FS, Mechoulam R. Antipsychotic effect of cannabidiol. *J Clin Psychiatry* 1995; 56: 485-486.

29. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev.* 2014; 5;3: CD009270.

30. Consroe P, Laguna J, Allender J, et al. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav*. 1991; 40: 701-708.

31. Zuardi AW, Cosme RA, Graeff FG, Guimarães FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. *J Psychopharmacol.* 1993a; 7: 82-88.

32. Borgwardt SJ, Allen P, Bhattacharyya S, et al. Neural basis of delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. *Biol Psychiatry.* 2008; 64: 966-973.

33. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr*. 2008; 30: 271-280.

34. Gong H Jr, Tashkin DP, Simmons MS, Calvarese B, Shapiro BJ. Acute and subacute bronchial effects of oral cannabinoids. *Clin Pharmacol and Ther*. 1984; 35: 26-32.

35. Zuardi AW, Hallak JE, Dursun SM, et al. Cannabidiol monotherapy for treatment-resistant schizophrenia. *J Psychopharmacol*. 2006; 20: 683-686.

36. Zuardi A, Crippa J, Dursun S, Morais S, Vilela J, Sanches R, et al. Cannabidiol was ineffective for manic episode of bipolar affective disorder. *J Psychopharmacol*. 2010; 24: 135-137.

37. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J. Med*. 2010; 362: 790-799.

38. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in subjects with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol*. 2016; 15: 270-8.

39. Braut-Boucher F, Braemer R, Bolline A, Kremers P. Comparative toxicological investigation of cannabidiol using two different cell culture systems. *Eur J Cell Biol*. 1986; 42: CT 17 (abstract).

40. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014; 55: 791–802.

16. INVESTIGATOR SIGNATURE PAGE

TITLE:	A Phase 2, Open-label, Dose-finding Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Pediatric Subjects with Treatment-Resistant Childhood Absence Seizures
PROTOCOL NUMBER:	INS011-17-103
PHASE OF STUDY:	Phase 2
PROTOCOL DATE:	06 May 2019
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.

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Principal Investigator Printed Name

_____ _____

Principal Investigator Signature **Date**