Clinical Study Protocol

Protocol Title:	**A multicenter, open-label, flexible dose study to assess the long-term safety of pharmaceutical Cannabidiol Oral Solution as an adjunctive treatment for pediatric subjects with a treatment-resistant seizure disorder who complete INS011-14-029 or Part A of INS011-15-054**
Protocol Number:	**INS011-14-030 / NCT02318602**
Date of Protocol:	**27 October 2014**
Amendment 1:	**11 December 2014**
Amendment 2:	**07 August 2015**
Amendment 3:	**08 April 2016**
Amendment 4:	**05 October 2016**
Administrative Change 1:	**01 November 2016**
Amendment 5:	**06 March 2017**
Product:	**Cannabidiol Oral Solution**
IND No.:	**123120**
Study Phase:	**3b**
Sponsor:	**Insys Development Company, Inc. 1333 South Spectrum Boulevard, Suite 100 Chandler, Arizona 85286, US**
Medical Monitor:	[redacted] **MD** [redacted] **US toll free:** [redacted]

Approval Signatures

PROTOCOL TITLE: A multicenter, open-label, flexible dose study to assess the long-term safety of pharmaceutical Cannabidiol Oral Solution as an adjunctive treatment for pediatric subjects with a treatment-resistant seizure disorder who complete INS011-14-029 or Part A of INS011-15-054

PROTOCOL NO: INS011-14-030, Amendment 5

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

[redacted] 07MAR2017
Date

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INSYS Development Company, Inc.

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Date

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INSYS Development Company, Inc.

SYNOPSIS

Name of Sponsor/Company:	Insys Development Company, Inc.
Name of Finished Product:	Cannabidiol Oral Solution
Name of Active Ingredient:	Cannabidiol
Title of Study:	A multicenter, open-label, flexible dose study to assess the long-term safety of pharmaceutical Cannabidiol Oral Solution as an adjunctive treatment for pediatric subjects with a treatment-resistant seizure disorder who complete INS011-14-029 or Part A in INS011-15-054
Phase:	3b
Protocol No:	INS011-14-030
Study centers:	Multicenter (approximately 10 sites), United States (US)

Study duration: Subjects will receive daily oral doses of Cannabidiol Oral Solution for approximately 48 weeks or until the investigational product is successfully approved for marketing in the US (whichever occurs earlier), inclusive of their treatment on the previous study. A Final Visit/Discontinuation Visit will be completed when the subject completes or stops the study. A Follow-up Visit will be completed 2 weeks after the Final Visit/Discontinuation Visit. For subjects enrolling from INS011-15-054, their visit entry in INS011-14-030 will be determined at the discretion of the sponsor and investigator. Combined study duration of INS011-15-054 and INS011-14-030 will not exceed approximately 48 weeks.

Objectives:

- To assess the long-term safety of Cannabidiol Oral Solution as an adjunctive treatment for subjects with treatment-resistant seizure disorders, including Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) or infantile spasms (IS).
- To establish the continued efficacy of Cannabidiol Oral Solution in maintaining seizure control in subjects with treatment-resistant seizures that previously completed INS011-14-029 or Part A (Visit 6) in INS011-15-054.
- To assess the global status of subjects taking Cannabidiol Oral Solution for an extended period of time determined by various qualitative assessments.
- To monitor for changes in plasma levels of Cannabidiol Oral Solution during long-term treatment of subjects with treatment-resistant seizure disorders, including LGS, DS or IS.

- **Methodology**: This is a multicenter, open-label study to assess the long-term safety and efficacy of Cannabidiol Oral Solution as adjunctive therapy for pediatric subjects with treatment-resistant seizure disorders, including LGS, DS, and IS. Subjects must complete 1 of the following studies to be eligible.
- Activities through Day 11 in INS011-14-029.
- Activities in Part A through Visit 6 in INS011-15-054.

Eligible subjects will also be medically stable without new, clinically significant comorbidities since the Screening Visit in their previous study.

Subjects should enroll in INS011-14-030 immediately upon completion of the Treatment Period in their previous study (to avoid interruption of the investigational product). If rollover does not occur within 2 weeks after completion of the Treatment Period in their previous study the subjects will need to complete a Screening Visit (Visit 1) to confirm continued eligibility. If rollover does occur within 2 weeks after completion of the Treatment Period in their previous study Day 11 for INS011-14-029. For subjects enrolling from INS011-15-054, there should be no interruption of greater than 2 weeks between completing treatment in INS011-15-054 and initiating treatment in INS011-14-030. All assessments for the previous study will be

completed prior to administration of the first dose of Cannabidiol Oral Solution in INS011-14-030. Data from the baseline visit in the subject's previous study will serve as the baseline for INS011-14-030 where applicable. Data collected at the Screening Visit (Visit 1) or Visit 2 (Day 1) of this study will also be analyzed as a baseline, whichever visit represents the first visit in the INS011-14-030 for each respective subject, and as described in Section 8.2.2.

In this study, all subjects will be dosed as follows:

- Subjects who completed INS011-14-029 will initiate this study on the dose with which they were being treated previously, unless tolerability issues were observed for a particular subject.
- Subjects who enroll from INS011-15-054 will continue treatment with the dose at which they were being treated previously, unless tolerability issues were observed for a particular subject.
- Dosing of the investigational product may be adjusted for an individual subject at any time as per Investigator opinion should tolerability issues arise.

Treatment with established antiepileptic drugs (AEDs) will continue without interruption and changes will be permitted as necessary based on safety concerns or changes in seizure control.

Treatment visits will be scheduled weekly at Visits 3 and 4, then monthly for 3 months, and then quarterly thereafter. All subjects will complete a Final Visit/Discontinuation Visit regardless of when they stop treatment/complete the study. A Follow-up Visit will occur 2 weeks after the Final Visit/Discontinuation Visit. For subjects enrolling from INS011-15-054, their visit entry in INS011-14-030 will be determined at the discretion of the sponsor and investigator. Combined study duration of INS011-15-054 and INS011-14-030 will not exceed approximately 48 weeks.

At each visit, a record of the incidence and severity of adverse events (AEs), treatment-emergent AEs (TEAEs), and Serious Adverse Events (SAEs) will be collected and this will serve as a primary outcome criterion for this study. Other safety-related parameters such as 12-lead ECG and hematology, chemistry, and urinary analyses will also be assessed at specified visits. Determination of trough plasma levels of cannabidiol and its 7-OH metabolite will be performed at each visit except at Visits 3 and 4. Information regarding diet (including ketogenic diet), time of the closest meal, and time of drug administration will be collected. This will support safety monitoring and establish the extent of variability during long-term treatment with the investigational product. For subjects taking clobazam, levels of clobazam and its major metabolite (norclobazam) will be measured if there are safety concerns. Seizure diaries will be collected to assess control of seizures (frequency, duration, and severity) for one week prior to each quarterly visit.

At each visit except Visits 3 and 4, the following qualitative assessments will be completed: Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression of Severity (CGI-S), Impact of Pediatric Epilepsy Scale (IPES), and Columbia-Suicide Severity Rating Scale (C-SSRS) if appropriate. The Vineland Adaptive Behavior Scales, Second Edition – Survey Interview Form including the Maladaptive Behavior Index (VABS) will be collected at Visit 2 and visit 10 or early termination. Subjects enrolled from INS011-15-054 will be excluded from IPES, VABS, and C-SSRS scores evaluation.

Planned number of subjects:	The study will include subjects who completed activities through Day 11 in INS011-14-029 or Part A (Visit 6) in INS011-15-054. The estimated maximum number of rollover subjects from these previous studies is as follows: • INS011-14-029: 60 subjects • INS011-15-054: 20 subjects If all subjects are eligible for and elect to continue into INS011-14-030, the population of this study will be a maximum of 80 subjects.
Main criteria for inclusion:	1. Completed activities through Day 11 in INS011-14-029 or Part A (Visit 6) INS011-15-054 2. Informed consent and assent (as applicable) of the subject

	and/or parent(s)/caregiver(s) in accordance with applicable laws, regulations, and local requirements 3. Medically stable in the opinion of the Investigator. a. Changes in background AEDs may occur during the study as discussed in Section 4.3. Care should be taken if patients are on other drugs metabolized by CYP enzymes. 4. A female subject is eligible to participate in the study if she is: a. Premenarchal, or b. Of childbearing potential with a negative serum pregnancy test at Screening (only for those subjects required to complete the Screening Visit) and a negative urine pregnancy test at Visit 2. If sexually active, she must fulfill 1 of the following requirements: i. Complete abstinence from intercourse ≥4 weeks prior to administration of the first dose of the investigational product, throughout the Treatment Period, and 4 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 4 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 diaphragm). 5. A sexually active male subject must use acceptable methods of contraception throughout the study and for 4 weeks completion of study participation or premature 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 diaphragm). 6. In the opinion of the Investigator, the subject and/or parent(s)/caregiver(s) are able to continue keeping accurate seizure diaries.
Main criteria for exclusion:	1. Experienced an anoxic episode related to study drug requiring resuscitation during their previous study. 2. Evidence of other clinically significant disease such as unstable hepatic, hematological, renal, cardiovascular, gastrointestinal, immunological, or pulmonary diseases or ongoing malignancies. 3. Compromised respiratory function or severe respiratory insufficiency. 4. Clinically significant abnormal laboratory values within the

	past 14 days, including: a. Liver function tests (LFTs) such as albumin, direct bilirubin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN). b. The investigator may deem the subject eligible if in the opinion of the investigator, the clinically significant abnormal laboratory values are deemed to be acceptable and to not have an impact on subject safety. 5. Inadequate supervision by parent(s)/caregiver(s). 6. For appropriate subjects, an affirmative answer to queries regarding active suicidal ideation with some intent to act but without a specific plan or active suicidal ideation with specific plan and intent on the C-SSRS assessment at the Screening Visit. Subjects who have significant findings for suicidal ideation as assessed by the C-SSRS must be referred to the Investigator for follow-up evaluation.
Test product, dose and mode of administration:	Cannabidiol Oral Solution: an oral solution containing pharmaceutical grade cannabidiol (nonplant-based). Subjects who completed INS011-14-029 will initiate this study on the dose with which they were being treated previously (10, 20, or 40 mg/kg/day administered in twice daily doses of 5, 10, or 20 mg/kg, depending on dose cohort). For subjects enrolling from INS011-15-054 their dose will be the same as in the previous study (maximum of 40mg/kg/day). The total daily dose (mg/kg/day) will be administered in two equal concentration doses (mg/kg) at 12-hour intervals. Dosing of the investigational product may be adjusted at any time based on investigators discretion, however maximum daily dose will not exceed 40 mg/kg/day. Subjects who will not continue to receive Cannabidiol Oral Solution under the Investigator IND Expanded Access Program may be tapered off based on Investigator's preference and subject's tolerability The investigator should ensure that the taper is planned in advance to allow sufficient time to complete the taper prior to Visit 10 at 48 weeks (±10 days).The date of entering the Expanded Access Program will be documented in the EDC. The timing of administration of the drug with regards to food should be consistent throughout the duration of the study.
Reference therapy, dose, and mode of administration:	Not applicable.
Endpoints • Incidence, type, and severity of AEs and SAEs associated with Cannabidiol Oral Solution as an adjunctive treatment for seizures • Changes from baseline in the previous study in vital signs • Changes from baseline in the previous study in ECG findings if appropriate • Changes from baseline in the previous study laboratory values (hematology, chemistry, and	

urinalysis)

- Trough (steady state) concentrations of Cannabidiol Oral Solution throughout approximately 48 weeks of continuous exposure, inclusive of the subject's treatment on their previous study

Efficacy-related Data to be Reported

- Frequency, duration, and severity of seizures (i.e., seizure control).
- Parent(s)/caregiver(s) CGI-I and CGI-S.
- Investigator CGI-I and CGI-SIPES, C-SSRS, and VABS scores, Subjects enrolled from INS011-15-054 will be excluded from IPES, VABS, and C-SSRS scores evaluation.

Criteria for evaluation: A record of the incidence and severity of treatment-emergent AEs (TEAEs) and SAEs throughout the study is the primary criterion. Other safety-related parameters such as 12-lead ECG and hematology, chemistry, and urinary analyses will also be assessed.

Plasma levels of cannabidiol and its 7-hydroxy (OH) metabolite will be evaluated (trough levels). For subjects taking clobazam, levels of clobazam and its major metabolite (norclobazam) will be measured if there are safety concerns.

Secondary outcome measures will include control of seizures (frequency, duration, and severity of seizures compared to baseline in the previous study), overall changes in global impression assessments by the Investigator and parent(s)/caregiver(s) (CGI-I and CGI-S), and change from baseline in IPES, VABS, and C-SSRS scores, Subjects enrolled from INS011-15-054 will be excluded from IPES, VABS, and C-SSRS scores evaluation.

Statistical methods: The sample size will be determined by the number of subjects that are eligible and elect to rollover from INS011-14-029 and INS011-15-054 into this study.

Data listings and univariate descriptive summary statistics (number and percentages) will be generated for TEAEs and SAEs. The AEs with missing onset dates or AEs with missing onset times occurring on the same day as the administration of investigational product will be summarized as TEAEs. Both AEs and SAEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA). Each verbatim term will be mapped to a lower level term, then to a preferred term (PT), and finally to a system organ class (SOC). The number and percentage of subjects with $\geq$1 TEAE for each SOC and preferred term will be summarized.

Laboratory analytes will be summarized as mean change from baseline to endpoint. Shift tables will also be produced describing changes from normal to abnormal (high and low) levels or abnormal (high and low) to normal levels.

For each continuous endpoint, descriptive statistics (number, mean, median, minimum, maximum, standard deviation [SD], and 95% confidence interval [CI]) will be generated. This analysis will be carried out for the change from baseline in frequency, severity, and duration of seizures, IPES, VABS, and C-SSRS scores, as well as parent(s)/caregiver(s) and Investigator CGI-I and CGI-S. Subjects enrolled from INS011-15-054 will be excluded from IPES, VABS, and C-SSRS scores evaluation.

Concentrations of cannabidiol and its 7-OH metabolite will be measured at each visit except Visits 3 and 4. A descriptive summary of observed blood concentrations (number, mean, median, SD, minimum value, and maximum value) will be displayed.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
$5\text{-}HT_{1a}$	5-hydroxytryptamine 1a
AE	adverse event
AED	antiepileptic drug
ADR	adverse drug reaction
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
β-hCG	β human chorionic gonadotropin
BUN	blood urea nitrogen
CB_1	cannabinoid receptor 1
CB_2	cannabinoid receptor 2
CBC	complete blood count
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
cGMP	current Good Manufacturing Practices
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
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
DNA	deoxyribonucleic acid

DS	Dravet syndrome
ECG	electrocardiogram
eCRF	electronic case report form
ED_{50}	median effective dose
EDC	electronic data capture
EEG	electroencephalogram
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IL-2	interleukin-2
IP	intraperitoneal
IPES	Impact of Pediatric Epilepsy Scale
IRB	Institutional Review Board
IV	intravenous
LFT	liver function test
LGS	Lennox-Gastaut Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NICE	National Institutes of Health and Care Excellence
NK	natural killer
OH	hydroxy
PCOS	polycystic ovarian syndrome
PK	pharmacokinetics
pKa	acid dissociation constant
PRO	patient reported outcome
PT	preferred term

RBCs	red blood cells
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCN1A	α subunit of the sodium channel, voltage-gated, type 1
SD	standard deviation
SMEI	severe myoclonic epilepsy of infancy
SOC	system organ class
SOP	standard operating procedures
$t_{1/2}$	half-life
TD_{50}	median tolerated dose
TEAE	treatment-emergent adverse event
Δ^9-THC	Δ^9-tetrahydrocannabinol
TLFs	tables, listings, and figures
UK	United Kingdom
ULN	upper limit of normal
US	United States
VABS	Vineland Adaptive Behavior Scale, Second Edition – Survey Interview Form including the Maladaptive Behavior Index
VNS	vagus nerve stimulation
WBCs	white blood cells
WHO-DD	World Health Organization's Drug-Dictionary

1.0 INTRODUCTION

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

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

1.1 Cannabidiol

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

Insys Development Company, Inc. (hereafter referred to as the Sponsor) has successfully manufactured a pharmaceutical grade, nonplant-based cannabidiol (Cannabidiol Oral Solution). It is manufactured in their current Good Manufacturing Practices (cGMP) manufacturing facility. This facility is approved by the Drug Enforcement Administration (DEA) and has been inspected by the Food and Drug Administration (FDA). This active pharmaceutical ingredient (API) is ≥99.5% pure,[6] can be consistently produced without the concern for contaminants, and will provide cannabidiol to responsibly treat epilepsy.

1.1.1 Mechanism of Action

The mode of action of cannabidiol is not fully understood. The drug substance manifests a low affinity for endogenous cannabinoid receptors 1 (CB_1) and 2 (CB_2). Cannabidiol acts primarily as an indirect antagonist of CB_1 and inhibits several CB_1-mediated Δ^9-THC effects.[7] It also stimulates the vanilloid receptor type 1[8] and modulates the μ- and δ-opioid receptors.[9] It may also increase plasma Δ^9-THC levels by inhibiting its hepatic microsomal metabolism by competitively binding proteins in the cytochrome P450 (CYP) oxidative system.[10] Finally, cannabidiol may modulate neuronal hyperexcitability through 1 or more of the following mechanisms:

- Bidirectional regulation of calcium homeostasis via the mitochondrial sodium/calcium exchanger[11]
- Agonistic properties at 5-hydroxytryptamine 1a ($5\text{-}HT_{1a}$) 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 cannabidiol is similar to that of other cannabinoids and mediated by hydroxylation by CYP proteins.[15] Its interactions with human drug metabolizing enzymes (as a substrate, inhibitor, or inducer) were recently reviewed.[16,17] Details of some interactions may be found below.

Cannabidiol is metabolized primarily in the liver by cytochrome P 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 2C19 (CYP2C19). The effect of cannabidiol on primary fetal rat hepatocyte viability was investigated.[18] In vitro, hepatocytes showed reduced cell viability, inhibited cell growth, and cytoplasmic alterations after 24 hours of exposure to cannabidiol at concentrations of 10^{-4} to 10^{-3} M. Markers of cell injury increased following treatment of cannabidiol at concentrations of 10^{-4} M (160% of control after 24 hours of exposure) and 5 x 10^{-5} M (220% of control after 72 hours). These results correspond to other studies showing that cannabidiol is a potent inhibitor of hepatic drug metabolism.[19,20,21] Specifically, cannabidiol inhibits CYP3A4, cytochrome P450 3A5 (CYP3A5), and cytochrome P450 1A1 (CYP1A1) in vitro.[22,23,24] It also appears to inhibit cytochrome P450 2C9 (CYP2C9)[25] and the transport protein p-glycoprotein.[26,27]

Cannabidiol likely inhibits drug metabolism when 1 of its metabolites binds to hepatic microsomal CYP proteins.[28,29,30,31] Hexobarbital is metabolized by CYP2C9 and the duration of sleep induced by hexobarbital may be used as a surrogate for drug metabolism. Using this outcome measure, it was shown that suppression of drug metabolism by cannabidiol diminished following repeated exposure to the drug substance in rodents.[32]

Clinically, oral intake of cannabidiol (100 mg every 4 hours for 5 to 12 days) produced a 36% lower clearance and 35% lower volume of distribution of hexobarbital in healthy volunteers.[33] Notably, this study also showed that liver function tests (LFTs) remained normal before and during cannabidiol ingestion. Cannabidiol also inhibited barbiturate metabolism in humans to an extent substantially greater than that observed for Δ^9-THC. Conversely, another study reported that oral dosing with cannabidiol (25 mg/kg) did not significantly affect the total clearance, volume of distribution, or terminal elimination half-life ($t_{1/2}$) of Δ^9-THC metabolites.[34] It has also been shown that suppression of drug metabolism by cannabidiol is diminished following repeated exposure to the drug substance.[35]

1.1.3 Nonclinical

1.1.3.1 Safety

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

- In a repeated-dose toxicity study, monkeys treated with oral cannabidiol (0, 30, 100, or 300 mg/kg/day), spermatogenesis was inhibited.[36] Another study reported abnormal sperm in animals exposed to cannabidiol and that paternal exposure to cannabidiol is associated with a lower impregnation rate, a 2.3-fold increase in fetal loss, and a 5.2-fold increase in postnatal loss.[37]

- Levels of FSH increased approximately 70% to 100% in Rhesus monkeys dosed with 100 and 300 mg/kg/day of cannabidiol.[38]

- Blood sampling following repeated daily injections of 5 mg/kg/day cannabidiol for 14 days in adult male Wistar rats showed decreased total leukocyte number and total numbers of T and B cells and T helper and T cytotoxic subsets.[39] This immunosuppressive effect did not affect the total numbers of natural killer (NK) and NK T cells that are responsible for the primary, nonspecific antiviral, and antitumor immune response. Mechanistically, 0.5 to 10 μM of cannabidiol suppressed interleukin-2 (IL-2) and interferon (IFN)-γ messenger ribonucleic acid (mRNA) expression, proliferation, and cell surface expression of the IL-2 receptor α chain in murine splenocyte cell suspensions.

- Human peripheral lymphocytes cultured with 3.2×10^{-6} M cannabidiol for 72 hours did not induce chromosomal aberrations.[40] Similarly, treatment with 20 to 250 μM cannabidiol did not induce unscheduled deoxyribonucleic acid (DNA) repair synthesis in cultured human fibroblasts.[41] Cultured lymphocytes harvested from prior *cannabis* users receiving oral doses of 1200 mg/day of cannabidiol for 20 days did not show an increase in chromosomal aberrations or sister chromatid exchange.[42]

- Intraperitoneal (IP) injection of 1 or 10 mg/kg/day into mice resulted in 2- to 6-fold increases in chromosomal and nuclear aberrations in bone marrow cells harvest from these mice.[43]

    - Conversely, human peripheral lymphocytes cultured with 3.2×10^{-6} M cannabidiol for 72 hours did not induce chromosomal aberrations.[44]

Similarly, treatment with 20 to 250 µM cannabidiol did not induce unscheduled DNA repair synthesis in cultured human fibroblasts.[45] Cultured lymphocytes harvested from prior *cannabis* users receiving oral doses of 1200 mg/day of cannabidiol for 20 days did not show an increase in chromosomal aberrations or sister chromatid exchange.[46]

- As described in Section 1.1.2, cannabidiol may also affect liver-mediated metabolism as a result of its interactions with CYP proteins and p-glycoprotein.

1.1.3.2 Efficacy in Epilepsy Animal Models

Plant-derived cannabidiol shows antiepileptic,[47] antipsychotic, antidystonic, anti-emetic, and anti-inflammatory properties in animal models.[48] These models support exploring the use of cannabidiol for the treatment of epilepsy.[49]

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

1.1.4 Clinical

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

1.1.4.1 Pharmacokinetics

Oral doses of cannabidiol (10 mg/kg/day) once daily for 6 weeks in patients with Huntington's disease results in mean weekly plasma concentrations of 5.9 to 11.2 µg/L.[51,52] The mean $t_{1/2}$ for cannabidiol is 24 and 31 hours when administered intravenously (IV) or inhaled, respectively, with a range of 18 to 33 hours.[53] Cannabidiol is cleared from plasma at rates between 960 and 1560 mL/min and the distribution volume is estimated to be approximately 30 L/kg.[53]

1.1.4.2 Overview of Safety

Clinical studies in various human populations indicate that cannabidiol has a favorable side-effect profile. Doses as high as 1500 mg are well tolerated.[54] No significant reactions or serious adverse events (SAEs) have been reported across a wide range of dosages and in both

acute and chronic settings. Bergamaschi et al.[17] recently reviewed the safety of cannabidiol in humans examined in 221 subjects across 21 studies. As detailed in the IB, no significant safety issues were reported.

Selected studies in which more detailed information regarding safety outcomes are reviewed in Section 1.1.4.2.1.

Regarding doses of cannabidiol that have been examined in other studies, daily doses of 200 to 300 mg cannabidiol (or potentially more) may be safe.[2,58] Clinical evaluation and therapeutic ranges of cannabidiol 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 cannabidiol range. Furthermore, between 300 and 1500 mg have been used in humans without toxicity or SAEs.[51,55,56,57]. Cannabidiol PK has not previously been studied in a pediatric population.

1.1.4.2.1 Selected Detailed Clinical Safety Data

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

- Ten (10) mg/kg daily dosing of cannabidiol was evaluated in a study of 15 subjects diagnosed with Huntington's disease.[51] Only 15 abnormal clinical laboratory values were associated with cannabidiol treatment; these were largely limited to 4 subjects and exhibited no obvious pattern. No significant or clinical differences in cannabidiol were observed in a *cannabis*-specific side-effect inventory.
- Chronic oral administration of 10 mg cannabidiol 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 patients.[2]
- Oral administration of cannabidiol 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.[2,58]
- Administration of single and repeated doses of cannabidiol 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.[59]
- Three (3) subjects with treatment-resistant schizophrenia have been dosed with 40 to 1280 mg/day of cannabidiol for up to 4 weeks without reporting side-effects.[60]

- Two (2) subjects diagnosed with bipolar affective disorder did not report adverse effects upon receiving 600 to 1200 mg/day of cannabidiol for up to 24 days.[61]

1.1.4.3 Efficacy in Human Epilepsy

While efficacy is not a primary endpoint for this study (see Section 2.0), several preliminary studies of cannabidiol report reductions in seizure activity for a significant subset of subjects.

Cannabidiol 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 8 subjects randomized to the active arm received 200 to 300 mg/day of cannabidiol or placebo for up to 4.5 months in addition to previously established antiepileptic drugs (AEDs).[2,58] Subjects tolerated cannabidiol well, with no signs of toxicity or serious side-effects. Four (4) of the 8 subjects receiving cannabidiol remained almost free of convulsive crises throughout the study and 3 others experienced partial improvement. The clinical condition of 7 subjects receiving placebo remained unchanged and 1 subject improved.

Parents of children with treatment-resistant epilepsy have sought cannabidiol-enriched *cannabis* for treatment.[4] In a survey, these parents reported dosages of cannabidiol ranging from <0.5 to 28.6 mg/kg/day, as per results from medical *cannabis* testing facilities. Sixteen (16; 84%) of the 19 parents eligible to respond to the survey reported a reduction in their child's seizure frequency while taking cannabidiol-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 cannabidiol: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.

1.1.5 Previous Studies with the Investigational Product

A Phase 1/2 study to examine the pharmacokinetics (PK), safety, and tolerability of Cannabidiol Oral Solution in a variety of treatment-resistant seizure disorders (INS011-14-029) is being conducted. The Sponsor has received an orphan drug designation for investigating Cannabidiol Oral Solution in the treatment of Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS). Phase 3 studies (INS011-14-024 and INS011-14-025,

respectively) are planned to examine the safety and efficacy of Cannabidiol Oral Solution in the treatment of seizures in LGS and DS subjects.

Subjects who completed INS011-14-029 or Part A in INS011-15-054 and satisfy the inclusion/exclusion criteria detailed in Section 3.4 are eligible to participate in this study.

1.2 Pediatric Treatment-Resistant Seizure Disorders

The clinical manifestations of epilepsy are periodic, uncontrolled, convulsive seizures. The highest incidence of epilepsy in North America and Europe is in the first 12 months of life when 90 to 212 cases per 100,000 individuals are diagnosed. Children diagnosed with various types of epilepsy have an increased risk (23% to 34%) of behavioral and cognitive symptoms and comorbidities.[62]

As recently reviewed,[62,63] current interventions for pediatric epilepsy patients include the following:

- AEDs
    - The FDA has approved multiple medications (i.e.clonazepam, felbamate, lamotrigine, topiramate, rufinamide, and clobazam) for adjunctive use in pediatric epilepsy. Although not approved in the US, other AEDs that may be used in this population include stiripentol.
- Resective surgery for specific types of drug-resistant focal epilepsy (e.g., Rasmussen encephalitis and tuberous sclerosis complex)
- Ketogenic diet or low-glycemic index diet
- Vagus nerve stimulation (VNS).

Safety and tolerability issues with current AED therapies include the following:

- Valproic acid: weight gain or loss, nausea and vomiting, pancreatitis, liver failure, thrombocytopenia, fetal anomalies if used in pregnancy, polycystic ovarian syndrome (PCOS), and hair loss
- Clobazam: irritability, sedation, hypotonia, and drooling
- Topiramate: decreased appetite, weight loss, decreased sweating, slowing of verbal processing, kidney stones, acidosis, and glaucoma
- Levetiracetam: behavior and mood issues.

Additionally, some currently approved AEDs have specific contraindications. For example, clobazam is excluded as a therapy for patients with significant liver disease or acute narrow angle glaucoma. Some AEDs also carry specialized warnings (e.g., serious skin reactions with clobazam and lamotrigine).

In addition to the above tolerability issues, 10% to 40% of patients with epilepsy are treatment-resistant.[64,65,66] The hallmark of treatment-resistance seizures is the failure of ≥2 AEDs to control them.[67] Patients diagnosed with LGS and DS are frequently treatment-resistant. These indications will be among those investigated in this study (among other treatment-resistant seizure disorders) and will also be examined in planned Phase 3 studies. Data from the current study will inform the dose of the investigational product to be examined in the Phase 3 studies.

1.2.1 Lennox-Gastaut Syndrome

A severe childhood epileptic encephalopathy, LGS represents an estimated 1% to 10% of all pediatric epilepsies. This pathology typically develops between 3 and 5 years of age, but can arise any time between 1 and 8 years of age.[68] According to the Commission on Classification and Terminology of the International League Against Epilepsy, LGS is characterized by the following:

- Multiple seizure types, including tonic, atonic, and atypical absence
    - Partial, myoclonic, and generalized tonic-clonic seizures may also be observed.
- An EEG pattern with diffuse and slow spike-and-wave complexes (<3 Hz) with paroxysmal fast rhythms of 10 to 12 Hz in sleep
- Cognitive dysfunction with psychomotor delay and neuropsychiatric problems
- Frequent lesional etiology
- Later onset than comparable pediatric epilepsies.

In the United Kingdom (UK), the National Institutes of Health and Care Excellence (NICE) guidelines (2012) recommend sodium valproate as first-line treatment for LGS, followed by lamotrigine (second-line), rufinamide or topiramate (third-line), and felbamate as a last therapeutic option. Typical treatment in the United States (US) follows a similar pattern, though there are no specific guidelines in this country due to the heterogeneity of patients. Each of FDA-approved AEDs for pediatric epilepsy include LGS as an approved indication in their labeling. Only approximately 10% of pediatric LGS patients undergo full seizure remission with currently available interventions.[69,70]

1.2.2 Dravet Syndrome

A genetic form of pediatric epilepsy, DS occurs in 1 of 20,000 to 40,000 live births. It was initially described in 1978 as severe myoclonic epilepsy of infancy (SMEI), and has a high rate (15%) of early mortality.[71] Seizures in DS patients typically begin at 5 to 8 months of age and are frequently associated with fever in the initial stage of the disease. Seizures may be of a variety of types, including:

- Generalized clonic
- Generalized tonic–clonic
- Atypical absence
- Myoclonic
- Focal, with or without secondary generalization
- Tonic (rarely).

By 2 years of age, many DS patients exhibit other neurologic symptoms, including cognitive deficits, lack of attention, and motor dysfunction.[72,73] 70% to 80% of patients diagnosed with DS exhibit identified mutations in the α subunit of the sodium channel, voltage-gated, type 1 (SCN1A) gene.[71,74,75] Such mutations are often used to confirm diagnosis.

In the UK, the NICE guidelines (2012) recommend sodium valproate or topiramate as first-line treatment for DS, followed by clobazam or stiripentol (second-line). Of the 6 AEDs that are FDA-approved for adjunctive use in pediatric epilepsy, none are labeled for the treatment of DS. In the US, clinicians may choose to utilize an AED off-label to treat patients with DS since there are no approved therapies or treatment algorithms. Typical treatment in the US is to maintain patients on a combination of valproate with or without topiramate, clobazam, or levetiracetam and to use benzodiazepines (e.g., clonazepam, diazepam, lorazepam, or midazolam) as rescue therapy. Regardless of the chosen treatment, most cases of DS are refractory to medical management and outcomes are generally poor.[76]

1.2.3 Study Population

Subjects diagnosed with treatment-resistant seizures to be enrolled in this study must satisfy the inclusion/exclusion criteria detailed in Sections 3.4.1 and 3.4.2.

Subjects will all receive the investigational product in an open-label setting. It is estimated that up to 80 subjects will enroll.

All subjects will be treated in an adjunctive setting.

1.3 Study Rationale

Treatment-resistant seizure disorders, including LGS,DS and IS, are life-time disorders that require prolonged exposure to medications to control seizures. This open-label study will assess the long-term safety and seizure control of Cannabidiol Oral Solution as an adjunctive therapy for the treatment of treatment-resistant seizures in pediatric subjects, including those with LGS, DS or IS.

Safety endpoints were a focus of INS011-14-029 and INS011-15-054, in which short-term dosing with the investigational product was examined. The current study will facilitate the monitoring of safety and tolerability during long-term treatment with the investigational product.

1.4 Risk-Benefit Analysis

As discussed in Sections 1.1.3 and 1.1.4, numerous nonclinical and clinical studies have examined other formulations of cannabidiol. Several areas of potential concern have been identified with the use of cannabidiol, 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 CYP2C19, and may inhibit these 2 isoenzymes, as well as having small effects on CYP3A5, CYP1A1, and CYP2C9
- Abnormal spermatogenesis
- Abnormal induction of FSH in males
- Potential downregulation of immune responses involving the T, B, T-helper, and T cytotoxic subsets of leukocytes and/or those dependent on IL-2 or IFN-γ.

Based on recent studies of cannabinoid administration in humans, controlled cannabidiol may be safe in humans and animals. However, further studies are needed to investigate these reported effects.

The concomitant medication guidelines and safety monitoring (clinical laboratory, ECG, vital signs, and physical and neurological examination assessments) planned for this study (see Sections 4.9 and 6.1) are intended to minimize these potential safety risks. Levels of cannabidiol and its 7-hydroxy (OH) metabolite in the plasma will also be monitored (see Section 6.2).

Stopping criteria for individual subjects will dictate termination of subject participation should a safety issue arise (see Section 3.4.3).

This study will allow subjects who previously completed INS011-14-029 or participated in INS011-15-054 and completed Part A (visit 6) continued access. This is particularly important for those who received therapeutic benefit in terms of seizure control during the previous studies. As reviewed in Section 1.2, patients with treatment-resistant seizure disorders continue to experience a significant unmet medical need despite ongoing treatment with currently available medications and procedures. Devinsky et al.[77] recently noted that treatment-resistant seizure disorders are particularly good candidates for cannabidiol intervention.

From a therapeutic perspective, the risk of exacerbating a subject's epilepsy symptoms will be minimized by examining the investigational product in an adjunctive setting in combination with the subject's established AED(s) treatment regime. Alternations may be made to the subject's AED background medication(s) as discussed in Section 4.3.

In addition to the potential therapeutic benefit noted above, Insys' pharmaceutical grade, nonplant-based 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.

1.5 Compliance

Each Investigator agrees that the study will be conducted according to the protocol, International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

2.0 STUDY OBJECTIVES

2.1 Objectives

- To assess the long-term safety of Cannabidiol Oral Solution as an adjunctive treatment for subjects with treatment-resistant seizure disorders, including LGS, DS or IS.
- To establish the continued efficacy of Cannabidiol Oral Solution in maintaining seizure control in subjects with treatment-resistant seizures that previously completedINS011-14-029 or participated in INS011-15-054 and complete Part A (Visit 6).
- To assess the global status of subjects taking Cannabidiol Oral Solution for an extended period of time determined by various qualitative assessments.
- To monitor for changes in plasma levels of cannabidiol and its 7-OH metabolite during long-term treatment of subjects with treatment-resistant seizure disorders, including LGS, DS or IS.

3.0 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a multicenter, open-label study to assess the long-term safety of Insys' pharmaceutical Cannabidiol Oral Solution as adjunctive therapy for pediatric subjects with treatment-resistant seizure disorders, including LGS, DS and IS. Plasma levels of cannabidiol and its 7-OH metabolite and efficacy (seizure control and qualitative assessments of subject global status) will also be evaluated, though the latter will not be analyzed as endpoints.

Subjects must complete 1 of the following studies to be eligible for the current study:

- Activities through Day 11 in INS011-14-029
- Activities through Part A (Visit 6) in INS011-15-054.

Eligible subjects will also be medically stable without new, clinically significant comorbidities since the Screening Visit in the subject's previous study and satisfy the inclusion/exclusion criteria in Sections 3.4.1 and 3.4.2.

Subjects should enroll in INS011-14-030 immediately upon completion of the Treatment Period in their previous study (to avoid interruption of the investigational product). Rollover should occur within 2 weeks after completion of the Treatment Period in their previous study or when appropriate. A Screening Visit may be required for subjects that do not rollover within 14 days of completing their previous study.

In this study, subjects will be dosed as described below.

- Subjects who completed INS011-14-029 will initiate this study on the dose with which they were being treated previously, unless tolerability issues were observed for a particular subject.
- Subjects who completed Part A in INS011-15-054 will continue treatment with the dose at which they were being treated previously, unless tolerability issues were observed for a particular subject.

Subjects will receive twice daily oral doses of Cannabidiol Oral Solution as described in Section 4.1 for approximately 48 weeks or until the investigational product is successfully approved for marketing in the US (whichever occurs earlier), inclusive of their treatment on the previous study. For subjects that completed INS011-14-029, 48 weeks of treatment would be completed under this protocol. For subjects that participated in INS011-15-054,

duration of treatment in INS011-14-030 will be based on the length of time they were enrolled in INS011-15-054 such that total duration of treatment in both studies combined will not exceed approximately 48 weeks. Subjects visit entry into INS011-14-030 will be determined at the discretion of the sponsor and the investigator.

The study will be terminated upon 1 of the following:

- The investigational product is successfully approved for marketing in the US
- Sponsor elects to terminate INS011-14-030.

Treatment with established background AEDs will continue without interruption and changes will be permitted as necessary based on safety concerns or due to changes in seizure control as described in Section 4.3.

As described in Table 1 and Section 5.0, visits will be scheduled at Week 1, Week 2, then monthly for 3 months, and then quarterly thereafter. A Screening Visit will be required for all subjects that do not rollover within 14 days of completing their previous study. All subjects will complete the Final Visit/ Discontinuation Visit regardless of when they stop treatment/complete the study. A Follow-up Visit will occur 2 weeks after the Final Visit/Discontinuation Visit.

At each visit, a record of the incidence and severity of adverse events (AEs), treatment-emergent AEs (TEAEs), and SAEs will be collected and this will serve as a primary outcome criterion for this study. Other safety-related parameters such as 12-lead ECG and hematology, chemistry, and urinary analyses will also be assessed at specified visits. Determination of trough plasma levels of cannabidiol and its 7-OH metabolite will be performed at each visit except Visits 3 and 4 (Week 1 and Week 2). This will support safety monitoring and establish the extent of variability during long-term treatment with the investigational product. For subjects taking clobazam, levels of clobazam and its major metabolite (norclobazam) will be measured if there are safety concerns. Seizure diaries will be reviewed to assess control of seizures (frequency, duration, and severity) throughout the duration of the study.

At each visit except Visits 3 and 4 (Week 1 and Week 2), qualitative assessments will be completed as specified in the Schedule of Events (Table 1). The Investigator Clinical Global Impressions of Improvement (CGI-I) and Clinical Global Impressions of Severity (CGI-S), will be completed for all subjects regardless of chronological and developmental age. Other qualitative assessments will be completed in an age-specific manner. This refers to developmental age, as discussed below. Specifically:

- The Impact of Pediatric Epilepsy Scale (IPES),[78,79] is validated for subjects who are 2 to 16 years of age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES. Subjects >18 years of chronological age will not complete the IPES.
- If appropriate, the Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered to access suicidality.

The risk of suicide may be evaluated using the C-SSRS for patients aged >=7 years. Clinical impression will be used for patients < 7 years and for patients aged >=7 years with development impairment for whom the C-SSRS would be inappropriate.

The assessments to be completed in this study are discussed in Section 6.0.

Subject safety will be monitored by a medical and safety data review as described in Section 3.2.

3.2 Medical and Safety Data Review

The medical and safety data review will be conducted throughout the study in parallel with continued subject recruitment, enrollment, and dosing. In addition, the pharmacokineticist and statistician may review, as appropriate. Additional experts may be consulted, as necessary.

3.3 Schedule of Events

The Schedule of Events may be found in Table 1.

Subjects should rollover from the previous study as soon as possible following completion of Day 11 activities (INS011-14-029) or when appropriate for INS011-15-054 to avoid interruption of the investigational product. A Screening Visit may be required for all subjects that do not rollover within 14 days of completing their previous study. The duration of each subject's treatment will be determined by the duration of treatment the subject received in their previous study as described in Section 3.1.

Visits will occur weekly for two weeks, monthly for 3 months, and then quarterly thereafter. A Screening Period (Visit 1) may be required for all subjects that do not rollover within 14 days of completing their previous study. All subjects will complete a Final Visit/Discontinuation Visit regardless of when they stop treatment/complete the study. Discontinuation may occur due to reasons discussed in Sections 3.1 and 3.4.3. A Follow-up Visit will occur 2 weeks after the Final Visit/Discontinuation Visit.

Table 1 Schedule of Events

Assessments[a]	Visit 1 (14 Day Screening Period[b])	Treatment Period						Final Visit / Discontinuation Visit[d] (Visit 10) Week 48 ±10 days[e] (if not conducted at a normally scheduled visit)	Follow-up Visit
		Visit 2 (Day 1[c])	Visit 3 (Week 1) ±3 days	Visit 4 (Week 2) ±3 days	Visits 5, 6, & 7 Monthly: (Weeks 4, 8 & 12) ±7 days	Visits 8, 9, Quarterly: (Weeks 24 and 36) ±10 days[d]			Two weeks after Final Visit / Discontinuation Visit (Visit 11) ±5 days
Obtain informed consent[f]	X	X							
Demographics	X	X							
Review of inclusion/exclusion criteria	X	X							
Medical and surgical history	X	X							
Assessment of current AEDs	X	X	X	X	X	X		X	X
Concomitant medications and procedures	X	X	X	X	X	X		X	
ECG	X	X						X	
Vital signs[g]	X	X	X	X	X	X		X	X
Laboratory values (hematology, chemistry)[h]	X	X				X		X	X
Urinalysis[i]	X	X				X		X	X
Pregnancy test[j]	X	X				X		X	X

Assessments[a]	Visit 1 (14 Day Screening Period[b])	Treatment Period						Final Visit / Discontinuation Visit[d] (Visit 10) Week 48 ±10 days[e] (if not conducted at a normally scheduled visit)	Follow-up Visit
		Visit 2 (Day 1[c])	Visit 3 (Week 1) ±3 days	Visit 4 (Week 2) ±3 days	Visits 5, 6, & 7 Monthly: (Weeks 4, 8 & 12) ±7 days	Visits 8, 9, Quarterly: (Weeks 24 and 36) ±10 days[d]			Two weeks after Final Visit / Discontinuation Visit (Visit 11) ±5 days
Physical examination and neurological examination[k]	X	X				X		X	X
Dispense (D), review (R), and collect (C) subject seizure and dosing diary[l]					D	D/R/C		R/C	
Dispense (D) and collect (C) study drug and review (R) dosing procedures		D/R	D/R/C	D/R/C	D/R/C	D/R/C		C	
Administer morning dose of study drug in the clinic		X				X			
AEs and SAEs	X	X	X	X	X	X		X	X
Blood draw for plasma levels		X			X	X		X	X

Assessments[a]	Visit 1 (14 Day Screening Period[b])	Treatment Period						Final Visit / Discontinuation Visit[d] (Visit 10) Week 48 ±10 days[e] (if not conducted at a normally scheduled visit)	Follow-up Visit
		Visit 2 (Day 1[c])	Visit 3 (Week 1) ±3 days	Visit 4 (Week 2) ±3 days	Visits 5, 6, & 7 Monthly: (Weeks 4, 8 & 12) ±7 days	Visits 8, 9, Quarterly: (Weeks 24 and 36) ±10 days[d]			Two weeks after Final Visit / Discontinuation Visit (Visit 11) ±5 days
Investigator and Parent(s)/careg iver(s) CGI-S[m]	X	X			X	X		X	X
Investigator and Parent(s)/careg iver(s) CGI-I[m]					X	X		X	X
IPES[n, o]		X			X	X		X	X
VABS[n, p]		X						X	
C-SSRS[q]	X	X			X	X		X	X
Reminders for next visit[s]	X	X	X	X	X	X			

[a] At Visits 2, 5, 6,7 8,9 and 10 all assessments are to precede administration of the morning dose of the investigational product (i.e., the subject should arrive for their study visit without having taken the morning dose of the investigational product). See Section 5.1 for more details.

[b] A Screening Period (Visit 1) will be required only for all subjects that do not rollover within 14 days of completing their previous study.

[c] Visit 2 (Day 1) may occur simultaneously with Day 11 from INS011-014-029 or within 14 days of Visit 1 (Screening Visit) for INS011-14-030. All assessments (except vital signs) completed within 14 days prior to administration of the first dose of Cannabidiol Oral Solution in INS011-14-030 may be used for Visit 2 (Day 1) (to avoid repetition of procedures).

[d] Subjects will receive two daily oral doses of Cannabidiol Oral Solution for approximately 48 weeks or until the investigational product is successfully approved for marketing in the US (whichever occurs earlier), inclusive of their treatment on the previous

study, unless they are discontinued due to a reason described in Section 3.4.3. After 12 weeks, study visits will be completed at a quarterly frequency; the definition of quarterly is every 12 weeks (e.g., Weeks 24 and 36).

[e] All subjects will complete the Final Visit/ Discontinuation Visit regardless of when they stop treatment/complete the study.

[f] The ICF must be completed prior to rollover into INS011-14-030.

[g] Vital signs to be assessed are blood pressure, pulse rate, respiratory rate, and temperature. They will be taken after a 5-minute supine rest and, if applicable, following simultaneously scheduled ECG measurements.

[h] Fasting is NOT required for collection of plasma levels, hematology and chemistry laboratory samples; whether subject was fasting at time of collection should be recorded in the eCRF. Laboratory assessments completed within 14 days prior to administration of the first dose of Cannabidiol Oral Solution in INS011-14-030 may be used for Visit 2 (Day 1) (to avoid repetition of procedures).

[i] Urinalysis will include macroscopic review; microscopic will be completed if indicated by macroscopic results. Urinalysis completed within 14 days prior to administration of the first dose of Cannabidiol Oral Solution in INS011-14-030 may be used for Visit 2 (Day 1) (to avoid repetition of procedures).

[j] The pregnancy test is only required for female subjects of childbearing potential. A serum pregnancy test is required at Screening (only for those subjects required to complete the Screening Visit) and urine pregnancy test for all other specified visits. Urine pregnancy tests completed within 14 days prior to administration of the first dose of Cannabidiol Oral Solution in INS011-14-030 may be used for Visit 2 (Day 1) (to avoid repetition of procedures).

[k] A full physical examination (general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities systems) with neurological examination (developmental age, mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait, and station) will be performed at the subject's first visit (Screening or Visit 2. The subject's developmental capabilities will be assessed as a part of the neurological examination (in a manner the Investigator sees fit) during the Screening Period (Visit 1) or Visit 2 (Day 1) only, whichever visit occurs first for each respective subject.
A brief neurological examination (mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait, and station) will be performed during other visits. All physical exams will also include an assessment of the subject's height and weight. Weight measurements at the quarterly visits may be used to calculate the subject's dose volume. Additional examinations may be performed at the discretion of the Investigator.

[l] Seizure diaries will be collected to assess control of seizures (frequency, duration, and severity) for one week prior to each quarterly visit. In addition, timing of the administration of the drug and timing and contents of the meals will be collected.

[m] For appropriate subjects will complete the CGI-I and CGI-S for themselves.

[n] For subjects who previously completed INS011-14-029, the IPES and VABS that are completed on Visit 2 (Day 1) of INS011-14-030 will serve as the baseline. Analysis will also be done using the Visit 2 (Day 1) data in INS011-14-030 as the baseline (see Section 8.2.2).

[o] The IPES is validated for subjects who are 2 to 16 years of (developmental) age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES. . Subjects enrolled from INS011-15-054 will be excluded from IPES evaluation.

[p] The VABS is validated for use in subjects from birth to 90 years of age. To be conducted at Visits 2 and 10. Subjects enrolled from INS011-15-054 will be excluded from VABS evaluation.

[q] The C-SSRS will only be completed for subjects for whom it is appropriate. The suggested age range for the pediatric version of the C-SSRS is from middle childhood (typically, around 7 years of age) through onset of adolescence (typically, through 11 years of age). However, in the face of cognitive delays, the tool can be suitable in older age groups. The appropriate adult version will be used in subjects 12 years of age and older. Subjects enrolled from INS011-15-054 will be excluded from C-SSRS scores evaluation.

[r] The Investigator or study center staff will remind the subject and/or parent(s)/caregiver(s) that the subject should not take the morning dose of the investigational product prior to assessments/clinic visit on the date of their quarterly study visits. The last dose of the investigational product prior to quarterly visits should be administered in the evening the day immediately prior. The subject and/or parents(s)/caregiver(s) will also be reminded that the date and time of the evening meal on the day prior to the quarterly study visits should be recorded in the subject seizure and dosing diary.

AE: adverse event; AED: antiepileptic drug; CGI-I: Clinical Global Impression of Improvement; CGI-S: Clinical Global Impression of Severity; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; eCRF: electronic case report form; ICF: informed consent form; IPES: Impact of Pediatric Epilepsy Scale; SAE: serious adverse event; VABS: Vineland Adaptive Behavior Scales, Second Edition – Survey Interview Form including the Maladaptive Behavior Index (VABS)

3.4 Selection of Study Population

The study will include subjects who completed activities through Day 11 in INS011-14-029 or Part A in INS011-15-054. The estimated maximum number of rollover subjects from these previous studies is as follows:

- INS011-14-029: 60 subjects
- INS011-15-054: 20 subjects

If all subjects are eligible for and elect to rollover into INS011-14-030, the population of this study will be a maximum of 80 subjects.

Each subject must satisfy all inclusion/exclusion criteria in Sections 3.4.1 and 3.4.2.

3.4.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria:

1. Completed activities through Day 11 in INS011-14-029 or completed Part A in INS011-15- 054.
2. Informed consent and assent (as applicable) of the subject and/or parent(s)/caregiver(s) in accordance with applicable laws, regulations, and local requirements.
3. Medically stable in the opinion of the Investigator.
4. Changes in background AEDs may occur during the study as discussed in Section 4.3. Care should be taken if patients are on other drugs metabolized by CYP enzymes.
5. A female subject is eligible to participate in the study if she is:
   - Premenarchal, or
   - Of childbearing potential with a negative serum pregnancy test at Screening (only for those subjects required to complete the Screening Visit) and a negative urine pregnancy test on Visit 2 (Day 1). If sexually active, she must fulfill 1 of the following requirements:
     i) Complete abstinence from intercourse ≥4 weeks prior to administration of the first dose of the investigational product, throughout the Treatment Period, and 4 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 4 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 diaphragm).

6. A sexually active male subject must use acceptable methods of contraception throughout the study and for 4 weeks completion of study participation or premature 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 diaphragm).
7. In the opinion of the Investigator, subject and/or parent(s)/caregiver(s) are able to continue keeping accurate seizure diaries.

3.4.2 Exclusion Criteria

Subjects will not be entered in the study for any of the following reasons:

1. Experienced an anoxic episode related to study drug requiring resuscitation during their previous study.
2. Evidence of other clinically significant disease such as unstable hepatic, hematological, renal, cardiovascular, gastrointestinal, immunological, or pulmonary diseases or ongoing malignancies.
3. Compromised respiratory function or severe respiratory insufficiency.
4. Clinically significant abnormal laboratory values within the past 14 days, including:
   - LFTs such as albumin, direct bilirubin, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN).
   - The investigator may deem the subject eligible if in the opinion of the investigator, the clinically significant abnormal laboratory values are deemed to be acceptable and to not have an impact on subject safety.
5. Inadequate supervision by parent(s)/caregiver(s).
6. For appropriate subjects, an affirmative answer to queries regarding active suicidal ideation with some intent to act but without a specific plan or active suicidal ideation with specific plan and intent on the C-SSRS assessment at the Screening Visit. Subjects who have significant findings for suicidal ideation as assessed by the C-SSRS must be referred to the Investigator for follow-up evaluation.

3.4.3 Subject Withdrawal

All subjects are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment.

The criteria for enrollment are to be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be withdrawn from the study and the Sponsor must be contacted. An exception may be granted in rare circumstances where there is a compelling safety reason to allow the subject to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor to allow the subject to continue in the study.

In addition, subjects will be withdrawn from the study in the following circumstances (i.e., stopping criteria):

- The Investigator decides that the subject should be withdrawn for safety
    - If the decision to remove the subject from the study is made because of an intolerable AE or a clinically significant laboratory value associated with the use of the investigational product, the investigational product is to be discontinued, appropriate measures taken, and the Sponsor notified immediately.
- Subject is unwilling to continue in the study and/or the subject or caregiver withdraw consent
- Lack of compliance with protocol
- Investigator or Sponsor stops the study for any reason
- Subject becomes pregnant
- Laboratory values demonstrate a subject serum ALT or AST level >3 times ULN (requires confirmation within 2 days)
- Laboratory values demonstrate a subject serum total bilirubin in excess of >2 times the ULN (requires confirmation within 2 days)
- Subject is enrolled in error
- Subject is lost to follow-up.
    - Lost to follow-up will be defined as a subject failing to attend planned study visits or to response to contacts by the study center staff contacts after

documented 2 attempts and for whom no other contact information is available.

Subjects who discontinue the study early will be asked to complete the Final Visit/Discontinuation Visit, with assessments to be completed as indicated in Table 1.

Subjects may elect to withdraw from study treatment with the possibility of completing remaining visits to allow for monitoring until end of study. All data taken through the subject withdrawing consent or the Investigator or Sponsor decision to discontinue the study, as well as data from the Final Visit/ Discontinuation Visit, will be collected for discontinued subjects.

Subjects who withdraw or are withdrawn from the study will not be replaced.

4.0 STUDY TREATMENTS

4.1 Treatments Administered

The starting dose of the investigational product will be determined by the study previously completed by the subject.

Subjects who completed INS011-14-029 will initiate this study on the dose with which they were being treated previously, unless tolerability issues were observed for a particular subject. Subjects who completed Part A in INS011-15-054 will continue treatment with the dose at which they were being treated previously unless a tolerability issue was observed for a particular subject.

The Sponsor has developed a dronabinol product, which has a similar chemical composition to that of Cannabidiol Oral Solution. The 2 compounds differ in that dronabinol has closed ring, while the ring is open in Cannabidiol Oral Solution. Data from a single-dose PK study of dronabinol showed a mean $t_{1/2}$ of 5.5 hours. This data supports the twice daily dosing of Cannabidiol Oral Solution.

The strength of the investigational product is discussed in Section 4.3.

Immediately after dosing, the subject will consume an adequate amount of water or clear liquid according to the age of the subject.

- For subjects aged <2 years, 4 ounces of water or clear fluid should be offered and the amount consumed recorded in the electronic case report form (eCRF).
- For subjects aged 2 to <12 years, 5 ounces of water should be offered and the amount consumed recorded in the electronic case report form (eCRF).
- For subjects aged ≥12 years, 8 ounces of water should be offered and the amount consumed recorded in the electronic case report form (eCRF).

The subject is not required to fast prior to or after dosing. However, the timing of meals with regards to drug administration should be consistent throughout the duration of the study.

Dosing of the investigational product may be increased or decreased based on efficacy and tolerability up to a maximum of 40 mg/kg/day.

The investigational product will be administered in an adjunctive setting and background AED medication(s) will be administered as described in Section 4.3.

4.1.1 Dose Adjustments

IP dose may be adjusted at the investigators discretion. Dose may be adjusted up or down based on efficacy, safety or tolerability. All dose changes must be clearly documented in the eCRF. Maximum dose must never exceed 40mg/kg/day.

4.1.2 Dose Tapering

If the subject is not going to continue to receive IPoffered under the Investigator IND Expanded Access Program, the subject may be tapered off Cannabidiol Oral Solution based on the investigator's preference and subject's tolerability. The investigator should ensure that the taper is planned well in advance to allow sufficient time to complete the taper prior to the Visit 10 at 48 weeks (±10 days). The date of entering the Expanded Access Program will be documented in the EDC.

4.2 Identity of Investigational Product

The active pharmaceutical ingredient (API) in Cannabidiol Oral Solution is a nonplant-based, pharmaceutical grade cannabidiol manufactured according to cGMP. It is an off-white to pale yellow resin or crystal substance that is soluble in several organic solvents with an acid dissociation constant (pKa) of 9.64. The solution is a clear, colorless to pale yellow to brown colored solution filled into a 10 mL amber glass bottle. More detailed information may be found in the IB.

4.2.1 Storage of the Investigational Product

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

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

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 1 business day of discovering such loss or theft.

Furthermore, all practitioners are prohibited from hiring employees who have been convicted of a drug-related felony or who have had a DEA registration denied or revoked.

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

The investigational product will be dispensed from a Schedule I licensed study center.

Study centers are required to provide complete information, including eCRFs 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.

4.3 Background Therapy

Subjects are allowed to remain on their established AEDs throughout the study. For any patient the ketogenic diet and VNS settings may also be adjusted.

Safety issues may be encountered that are associated with concomitant administration of the investigational product with the subject's established AEDs that necessitate an alteration in AED medication. **AED medication(s), including stopping or starting medication(s), may be adjusted throughout the trial to maximize seizure control based on tolerability as judged by the investigator.**

The Statistical Analysis Plan (SAP) will address how changes in AED medication(s) will be addressed from a biostatistical perspective.

4.4 Packaging and Labelling

A description of the drug product may be found in Table 2. The investigational product will be supplied in either 10 mL or 30 mL amber glass containers of a 300 mg/mL strength.

Table 2 Description of Drug Product

Non-proprietary or common name of drug product	Cannabidiol Oral Solution, 300 mg/mL
Dosage form	Oral solution
Strength	300 mg/mL

The investigational product will be clearly marked according to FDA and/or ICH requirements regarding use for clinical study investigation only and will be labeled with the

investigational product name, study reference number, and storage conditions. It is the responsibility of the Investigator to ensure that accurate accountability records are maintained throughout the study. Study center staff will dispense the investigational product according to the handling instructions.

4.5 Selection of Doses in the Study

For this study, twice daily oral dosing will be initiated as detailed in Section 4.1 based on dosing in the subject's previous study.

Dose reductions of the investigational product may occur due to safety or tolerability concerns as described in Section 4.1.1. and Section 4.1.2. Dosing of the investigational product may also be increased (up to maximum 40 mg/kg/day) for an individual subject as per Investigator opinion if there is reason to believe that it is beneficial for the patient.

4.6 Selection and Timing of Dose for Each Subject

Subjects will receive the investigational product twice daily as descried in Section 4.1.

The subject and/or parent(s)/caregiver(s) will record the date and time for all administrations of the investigational product for one week prior to each quarterly visit in the subject seizure/dosing diary. On the seizure/dosing diaries parent(s)/caregiver(s) will also record the frequency, duration, and severity of seizures for one week prior to each quarterly visit.

Administration of the investigational product with regards to timing of meals should be consistent throughout the study.

It is recommended that sites call the subject and/or parent(s)/caregiver(s) to remind them to start recording seizures and dosing at one week prior to each quarterly visit.

4.7 Method of Assigning Subjects to Treatment Group

Subjects will be allocated to a dose of the investigational product based on their dosing in the previous studies as described in Section 4.1.

4.8 Blinding

The study is open-label; no blinding will be performed.

4.9 Prior and Concomitant Treatments

4.9.1 Excluded Medications and Foods

During the study, subjects are not to receive the following:

- Any cannabinoids (cannabidiol, Δ^9-THC, or marijuana)

- Any other investigational drug or investigational device.

Although they are not prohibited, subjects taking concomitant medications may require that the subject is monitored with special care to identify any AEs arising due to the potential for altered drug metabolism. This is discussed in detail in Section 6.1.1.1.

4.9.2 Allowed Medications

Any medications (other than those excluded by the protocol, see Section 4.9.1) that the Investigator considers necessary for a subject's welfare may be given at the Investigator's discretion.

Subjects will remain on established AEDs throughout the duration of the study except as described in Section 4.3. Typical AEDs for treatment-resistant seizure disorders are discussed in Section 1.2, but background AED medication(s) are not limited to those referenced in this protocol.

4.10 Treatment Compliance

The subject seizure and dosing diary will include a record of the date and time of each administration of the investigational product. Diary data will be collected for one week (7 days) prior to each quarterly visits.

Subjects exhibiting poor compliance should be counseled on the importance of good compliance to the study dosing regimen. Noncompliance is defined as taking <80% or >120% of the investigational product during any evaluation period (i.e., visit to visit).

Any departures from the intended regimen must be recorded in the eCRF.

4.11 Study Medication Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate record of the receipt, distribution, and collection (of unused supplies)

of all investigational product using the Drug Accountability Form. These forms must be available for inspection at any time.

All supplies of the investigational product 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 designee.

If the study is terminated, discontinued, suspended, or completed, all 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 in regards to the accountability of Schedule I medications will be followed (e.g., prevention of diversion).

5.0 STUDY PROCEDURES

Prior to performing any study related procedures or assessments, the Investigator will ensure that the subject and/or their parent(s)/caregiver(s) (if applicable) provides written informed consent and a pediatric subject provides assent (as appropriate). Subjects and their parent(s)/caregiver(s) (if applicable) will receive a copy of the informed consent form (ICF) and assent form for review and must provide fully informed consent prior to study participation.

The consent process must be conducted and the ICF signed before any study procedures.

See Section 9.3 for guidelines regarding subject consent and assent.

5.1 Screening Period (Visit 1)

Subjects that do not rollover within 14 days of completing their previous study (INS011-14-029) will be required to complete a Screening Visit. Subjects who enroll after participating in INS011-15-054 will not need to complete a Screening Visit if less than 14 days has elapsed between dosing.

The following procedures will be completed only after obtaining informed consent:

- Review of inclusion and exclusion criteria (see Sections 3.4.1 and 3.4.2)
- Record concomitant medications and concomitant procedures
- Obtain a 12-lead ECG
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements)
- Draw blood samples for hematology and chemistry (fasting NOT required) and record whether subject was fasting at time of collection in the eCRF
- Obtain a urine sample for urinalysis
- Obtain a blood sample for serum pregnancy test in female subjects of childbearing potential
- Perform a complete physical examination (see Section 6.1.5.2), including height and weight

- Perform a neurological examination (see Section 6.1.5.2), including assessment for developmental capabilities
- Record demographic data
- Record medical and surgical history
- Record recent medication history including current AEDs, vitamins, herbal preparations, blood products, and over-the-counter drugs
- Record AEs and SAEs
- Administer Investigator CGI-S
- Administer parent(s)/caregiver(s) CGI-S
    - When appropriate, subjects will complete the CGI-S for themselves.
- Administer C-SSRS (if appropriate).

5.2 Treatment Period

Subjects that completed INS011-14-029 will complete this study through the 48 week visit, unless they are discontinued due to a reason described in Section 3.4.3, or until the investigational product is successfully approved for marketing in the US (whichever occurs earlier). For subjects that participated in INS011-15-054 will participate through the Week 48 visit unless they are discontinued due to a reason described in Section 3.4.3, or until the investigational product is successfully approved for marketing in the US (whichever occurs earlier); however, the combined treatment duration in INS011-14-030 and INS011-15-054 will not exceed approximately 48 weeks

At Visits 2, 8, and 9, all assessments are to precede administration of the morning dose of the investigational product. Specifically, the subject will NOT receive the investigational product on the morning of Visits 2, 8, and 9 UNTIL all assessments have been completed. The morning dose of the investigational product should be administered following completion of all assessments.

Given the timing of study assessments in regards to administration of the investigational product and the twice daily dosing of this medication, all visits requiring in-clinic dose administration will preferably be scheduled in the morning. Ideally, all assessments should be completed before 12 PM (noon) in the time zone of the study center to adhere as closely as possible to the 12-hour interval for dosing (see Section 4.6).

5.2.1 Visit 2 (Day 1)

Since Day 11 for INS011-14-029 may represent the first visit of this study, activities that have been carried out in the previous protocol will not be repeated and the data will be used in the analysis of both studies provided the assessments are completed within 14 days prior to administration of the first dose of Cannabidiol Oral Solution in INS011-14-030 (to avoid repetition of procedures). Similarly, all assessments completed during the Screening Period (Visit 1), and within 14 days prior to administration of the first dose of Cannabidiol Oral Solution in INS011-14-030, may be used for the Visit 2 (Day 1), except vital signs.

If not already completed in the past 14 days, the following procedures will be completed PRIOR to administration of the morning dose of the investigational product:

- Obtain informed consent
    - The ICF must be completed prior to any procedures.
- Review of inclusion and exclusion criteria (see Sections 3.4.1 and 3.4.2).
- Record concomitant medications and concomitant procedures.
- Obtain a 12-lead ECG.
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements). Vital signs must be assessed regardless of date of last collection.
- Draw blood samples for hematology and chemistry (fasting NOT required) and record whether subject was fasting at time of collection in the eCRF.
- Obtain a urine sample for urinalysis.
- Obtain a urine sample for β human chorionic gonadotropin (β-hCG) pregnancy test in female subjects of childbearing potential.
- Complete blood draw for plasma levels.
- Perform a complete physical examination (see Section 6.1.5.2), including height and weight.
- Perform a brief neurology examination (see Section 6.1.5.2).
- Administer morning dose of the investigational product in the clinic.
- Record demographic data.
- Record medical and surgical history.

- Record and review current AEDs
- Dispense investigational product
- Review of dosing procedures for the investigational product
- Record AEs and SAEs
- Administer Investigator CGI-S
- Administer parent(s)/caregiver(s) CGI-S
    - When appropriate, subjects will complete the CGI-S for themselves.
- Administer IPES
    - The IPES is validated for subjects who are 2 to 16 years of (developmental) age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES.
- Administer VABS
    - The VABS is validated for use in subjects from birth to 90 years of age.
- Administer C-SSRS (if appropriate)
- Remind subject/parent(s)/caregiver(s) of next scheduled visit

5.2.2 Visits 3 and 4 (Weeks 1 and 2) ±3 days

The following procedures will be completed:

- Record concomitant medications and concomitant procedures.
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements).
- Record recent medication history including current AEDs, vitamins, herbal preparations, blood products, and over-the-counter drugs.
- Dispense and collect investigational product.
- Review of dosing procedures for the investigational product.
- Record AEs and SAEs.
- Remind subject/parent(s)/caregiver(s) of next scheduled visit.

5.2.3 Visits 5 and 6 (Monthly Visits) ±7 days

Subjects will complete Visits 5 and 6 monthly at Weeks 4 and 8.

The following procedures will be completed:

- Record concomitant medications and concomitant procedures
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements)
- Record recent medication history including current AEDs, vitamins, herbal preparations, blood products, and over-the-counter drugs
- Complete blood draw for plasma levels
- Draw blood samples for hematology and chemistry (fasting NOT required).
- Dispense and collect investigational product
- Review of dosing procedures for the investigational product
- Record AEs and SAEs
- Administer Investigator CGI-I and CGI-S
- Administer parent(s)/caregiver(s) CGI-I and CGI-S
    - When appropriate, subjects will complete the CGI-I and CGI-S for themselves.
- Administer IPES
    - The IPES is validated for subjects who are 2 to 16 years of (developmental) age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES.
- Administer C-SSRS (if appropriate)
- Remind subject/parent(s)/caregiver(s) of next scheduled visit.

5.2.4 Visit 7 (Monthly Visit) ±7 days

Subjects will complete Visit 7 at Week 12.

The following procedures will be completed:

- Record concomitant medications and concomitant procedures

- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements)
- Dispense subject seizure and dosing diary
    - Re-education of the parent/caregiver and/or subject regarding diary completion will be conducted. Diary data will be collected for one week (7 days) prior to the next visit.
- Record recent medication history including current AEDs, vitamins, herbal preparations, blood products, and over-the-counter drugs
- Complete blood draw for plasma levels
- Dispense and collect investigational product
- Review of dosing procedures for the investigational product
- Record AEs and SAEs
- Administer Investigator CGI-I and CGI-S
- Administer parent(s)/caregiver(s) CGI-I and CGI-S
    - When appropriate, subjects will complete the CGI-I and CGI-S for themselves.
- Administer IPES
    - The IPES is validated for subjects who are 2 to 16 years of (developmental) age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES.
- Administer C-SSRS (if appropriate)

5.2.5 Visits 8 and 9 (Quarterly Visits) ±10 days

Subjects will complete Visits 8 and 9 quarterly (every 3 months) at Weeks 24 and 36.

The following procedures will be completed:

- Record concomitant medications and concomitant procedures
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements)

- Obtain a urine sample for serum β-hCG pregnancy test in female subjects of childbearing potential
- Draw blood samples for hematology and chemistry (fasting NOT required) and record whether subject was fasting at time of collection in the eCRF
- Obtain a urine sample for urinalysis
- Complete blood draw for plasma levels
- Perform physical examination (see Section 6.1.5.2), including height and weight
- Perform a brief neurology examination (see Section 6.1.5.2)
- Review subject seizure and dosing diary and collect completed pages
    - Re-education of the parent/caregiver and/or subject regarding diary completion will be conducted as needed in the opinion of the Investigator.
- Dispense new subject seizure and dosing diary
    - Diary data will be collected for one week (7 days) prior to the next visit.
- Administer morning dose of the investigational product in the clinic.
- Record recent medication history including current AEDs, vitamins, herbal preparations, blood products, and over-the-counter drugs
- Dispense and collect investigational product
- Review of dosing procedures for the investigational product
- Record AEs and SAEs
- Administer Investigator CGI-I and CGI-S
- Administer parent(s)/caregiver(s) CGI-I and CGI-S
    - When appropriate, subjects will complete the CGI-I and CGI-S for themselves.
- Administer IPES
    - The IPES is validated for subjects who are 2 to 16 years of (developmental) age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES.

- Administer C-SSRS (if appropriate)
- Remind subject/parent(s)/caregiver(s) of next scheduled visit. The subject/parent(s)/caregiver(s) should be reminded that the morning dose of the investigational product should not be administered prior to study assessments/clinic visit on the date of their next study visit and to record the date and time of the evening meal on the day prior to the next study visit.

5.3 Final Visit/Discontinuation Visit (Visit 10) ±10 days

Each subject will complete a Final Visit/Discontinuation Visit regardless of when they complete/stop the study. Should a subject's participation be terminated according to study stopping criteria (see Section 3.4.3), this will be considered a Discontinuation Visit. For both, the following procedures will be completed:

- Record recent medication history including current AEDs, vitamins, herbal preparations, blood products, and over-the-counter drugs
- Record concomitant medications and concomitant procedures
- Obtain a 12-lead ECG
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements)
- Draw blood samples for hematology and chemistry (fasting NOT required) and record whether subject was fasting at time of collection in the eCRF
- Obtain a urine sample for urinalysis
- Obtain a urine sample for serum β-hCG pregnancy test in female subjects of childbearing potential
- Perform physical examination (see Section 6.1.5.2), including height and weight
- Perform a brief neurology examination (see Section 6.1.5.2)
- Review and collect subject seizure and dosing diary and collection of completed pages, if applicable
    - Diary data will be collected for one week (7 days) prior to Visit 10.
- Collect investigational product
- Record AEs and SAEs

- Complete blood draw for plasma levels
- Administer Investigator CGI-I and CGI-S
- Administer parent(s)/caregiver(s) CGI-I and CGI-S
    - When appropriate, subjects will complete the CGI-I and CGI-S for themselves.
- Administer IPES
    - The IPES is validated for subjects who are 2 to 16 years of (developmental) age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES.
- Administer VABS
    - The VABS is validated for use in subjects from birth to 90 years of age.
- Administer C-SSRS (if appropriate).

5.4 Follow-up Visit (Visit 11) ±5 days

All subjects will complete a Follow-up Visit 2 weeks (±5 days) after the Final Visit/Discontinuation Visit. The following activities will be completed:

- Record recent medication history including current AEDs, vitamins, herbal preparations, blood products, and over-the-counter drugs
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature measurements)
- Draw blood samples for hematology and chemistry (fasting NOT required) and record whether subject was fasting at time of collection in the eCRF
- Obtain a urine sample for urinalysis
- Obtain a urine sample for serum β-hCG pregnancy test in female subjects of childbearing potential
- Perform physical examination (see Section 6.1.5.2), including height and weight
- Perform a brief neurology examination (see Section 6.1.5.2)
- Record AEs and SAEs

- Complete blood draw for plasma levels
- Administer Investigator CGI-I and CGI-S
- Administer parent(s)/caregiver(s) CGI-I and CGI-S
    - When appropriate, subjects will complete the CGI-I and CGI-S for themselves.
- Administer IPES
    - The IPES is validated for subjects who are 2 to 16 years of (developmental) age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES.
- Administer C-SSRS (if appropriate).

6.0 SAFETY, PLASMA LEVEL, AND EFFICACY ASSESSMENTS AND ENDPOINTS

6.1 Safety

A central objective of this study is to investigate the safety and tolerability of the investigational product. This will be done by assessment of the following:

- AEs
    - Safety evaluation will consist of TEAEs and SAEs graded according to the Medical Dictionary for Regulatory Activities (MedDRA), including deaths. This will be captured at every subject visit to the study center. Additionally, standard laboratory tests (hematology, chemistry, and urinalysis as detailed in Section 6.1.4), 12-lead ECGs, physical and neurological examinations, and assessment of vital signs will be performed as indicated in Table 1.
- Clinical chemistry and hematology laboratory results
- Urinalysis
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, and respiratory rate)
- Physical and neurological examinations
- C-SSRS (if appropriate).

6.1.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product. It does not necessarily have a causal relationship with this treatment.

Seizures should not be considered an AE unless they differ significantly from the subjects' baseline. The onset of a new seizure type, as well as an injury incurred as a result of any seizure should be recorded as an AE.

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death

- Is life-threatening
    - This requires that the subject be at a risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Other medically significant events, which do not meet any of the criteria above, but may jeopardize the subject and may require medical or surgical intervention to prevent a serious outcome listed in the definition above (e.g., blood dyscrasias such as anemia requiring blood transfusion).

An adverse drug reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose. An unexpected ADR is defined as any adverse reaction, the nature of which is not consistent with the applicable product information.

The Investigator is responsible for recording all AEs observed during the study through the Follow-up Visit. Each AE will be evaluated for duration, severity, frequency, seriousness, and causal relationship to the study treatment. Action taken with the study treatment and outcome will also be recorded.

Definitions for severity and causal relationship to the study treatment are presented below.

Severity

The severity of the AE will be characterized as mild, moderate, or severe according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.

Relationship

The Investigator will assess the causal relationship of an AE to the investigational product and characterize the AE as unrelated, unlikely, possible, probable, or unknown (unable to judge). The following definitions of causality will be used:

- Events can be classified as "unrelated" if there is not a reasonable possibility that the study medication caused the AE.
- An "unlikely" relationship suggests that only a remote connection exists between the investigational product and the reported AE. With this classification, other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.
- A "possible" relationship suggests that the association of the AE with the study medication is unknown; however, the AE is not reasonably supported by other conditions.
- A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE. Other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable (e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation).

The frequency of each observed event will be recorded. Clinical actions taken as a result of an AEs include pausing, stopping, or delaying dosing of the investigational product. If applicable, the resolution of each observed AE will also be recorded; unresolved AEs at the time of subject discontinuation will be noted as such.

6.1.1.1 Monitoring of AEs Potentially Related to Drug Metabolism

Cannabidiol inhibits drug metabolism mediated by a subset of CYP proteins (see 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, or CYP1A1 or by p-glycoprotein with special care. Medication(s) that is/are inhibitor(s) or inducer(s) or sensitive substrates of CYP3A4 should be monitored with special care.

The CYP proteins noted above metabolize a selection of clinically important AEDs. As such, subjects should be monitored for AEs that may be related to a change in the metabolism of background AEDs. These may include:

- Increases in liver enzymes
- Increases in side effects associated with background AEDs
- Development of new side effects associated with background AEDs.

Similarly, several AEDs are known inducers of CYP3A4.[24] As such, their use may result in alterations in the level of the investigational product. Plasma levels of cannabidiol and 7-OH cannabidiol will be assessed as described in Section 6.2.

The Investigator may choose to assess plasma levels of background AEDs with which the subject is being treated should AEs arise that may be due to altered metabolism of these medications (see above). As noted in Section 4.3, decisions to alter background AED medications and dosing due to safety concerns will be considered on a case by case basis.

6.1.2 Reporting of AEs

The AEs and SAEs will be assessed at all study visits. As noted in Section 6.1.6, endpoints for this study include the AE/SAE record for each subject.

At each visit, information regarding AEs will be elicited from subjects by questioning conducted by the study center staff and the subject record will be reviewed with the parent(s)/caregiver(s) at each visit. The AEs and SAEs will be assessed at study visits according to the schedule indicated in Table 1. As noted in Section 6.1.6, endpoints for this study include the AE and SAE record for each subject.

All AEs, regardless of severity or when they occur, are to be recorded on the appropriate AE pages (either serious or nonserious) in the eCRF. The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome, and relationship to the investigational product. Each event should be recorded separately.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the investigational product, must be reported immediately (within 24 hours of the study center's first knowledge of the event) by fax to the Sponsor or designee.

The Sponsor contact information is listed below:

[redacted] RPh
[redacted]
Insys Development Company, Inc.
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

All SAEs will be recorded on the SAE Report Form, entered into the electronic data capture (EDC) system, and recorded in the source documents. The Investigator must complete, sign, and date the SAE Report Form, check that the data are consistent, and send a copy (within 24 hours, preferably by fax) to the Sponsor or designee list above.

The report will contain as much available information concerning the SAE to enable the Sponsor or designee to file a report, which satisfies regulatory reporting requirements. In addition to the initial 24-hour report, a completed, separate SAE Report Form is to be sent to the Sponsor or designee via fax or mail within 48 hours of the event. These timelines apply to initial reports of SAEs and to all follow-up reports.

Criteria for documenting the relationship to the investigational product, severity, and outcome will be the same as those previously described.

All SAEs that are spontaneously reported within 30 days of a subject's last visit are to be collected and reported as previously described.

The information must include at least the following:

- Investigational product
- Study name and code
- Name, address, fax number, email, and telephone number of the reporting Investigator
- Subject identification number, initials, and demographics (gender and date of birth)
- Clinical event
- Description of the AE, including
    - Date of onset
    - Treatment (drug, dose, dosage form)

- Preliminary classification of causal relationship by the Investigator.
- Measures taken (i.e., action taken regarding investigational product in direct relationship to the AE)
- Outcome

- If the AE was fatal or life-threatening
- Cause of death (and whether or not the death was related to investigational product)
- Autopsy findings (if available).

In the case of fatal or life-threatening events, please also immediately report by telephone to the Sponsor or designee.

Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor or designee and the original placed in the SAE section of the eCRF binder.

In medical emergencies, the Investigator should use medical judgment and remove the subject from immediate hazard. The Sponsor or designee will be notified regarding the type of emergency and course of action taken and the procedures for SAE reporting will be followed, if necessary.

During a subject's participation in the study, the Investigator or institution will provide adequate medical care for any AEs, including clinically significant laboratory values related to the study. The Investigator or institution should inform a subject when medical care is needed for an intercurrent illness (clinic, laboratory results, or otherwise) which in the opinion of the Investigator should receive medical follow-up.

6.1.2.1 Reporting of SAEs to Regulatory Authorities and Investigators

The Investigators will be responsible for submission of SAEs as required to their Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The Investigators should provide written documentation of IRB notification for each report to the Sponsor or designee. The Sponsor or designee will ensure that all SAEs are reported to the appropriate regulatory authorities.

Any additional local IRB/IEC reporting requirements for SAEs should be observed by the study center.

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

6.1.3 Follow-Up of AEs

Any AEs observed will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. All AEs that occur after the subject completed a clinical study should also be reported to the Sponsor or designee within 30 days of the last administration of the investigational product.

6.1.4 Clinical Laboratory Evaluations

All clinical laboratory tests will be reviewed for results of potential clinical significance throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

The following laboratory tests will be assessed at the time points specified by Table 1.

- Hematology: complete blood count (CBC) with differential, including platelet count, neutrophils, lymphocytes, eosinophils, basophils, monocytes, hemoglobin, and hematocrit
- Serum chemistry: total protein, albumin, creatinine, blood urea nitrogen (BUN), uric acid, total bilirubin, direct bilirubin, alkaline phosphatase, FSH, AST, ALT, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Urinalysis: specific gravity, pH, color, and presence of white blood cells (WBCs), red blood cells (RBCs), and proteins
- β-hCG in urine (pregnancy test)

LFTs (e.g., albumin, direct and total bilirubin, AST, and ALT) will be closely monitored to identify any damage that could be induced by the investigational product.

Levels of FSH will be monitored as a potential surrogate outcome for gametocyte damage.

Laboratory values outside the reference limits suspected to be of any clinical significance will be repeated. Subjects in whom suspected clinical significance is confirmed will either not be included or if already enrolled will be followed until normalization or for as long as the Investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the Investigator. Further details are provided in the Laboratory Manual.

6.1.4.1 Central Laboratory

Clinical laboratory tests will be analyzed centrally. Refer to the Laboratory Manual for information regarding collection, processing, and analysis of samples.

6.1.5 Vital Signs, Physical Findings and Other Safety Assessments

Vital signs, physical findings, and other safety assessments will be reviewed for results of potential clinical significance throughout the study. The Investigator will evaluate any changes. If the Investigator determines that a safety assessment is clinically significant, it is considered an AE. However, if the finding is consistent with the subject's current diagnoses, it may be documented accordingly.

6.1.5.1 Vital Signs

Vital signs (including blood pressure, pulse rate, respiratory rate, and temperature) will be recorded at the time points specified by Table 1.

If clinically significant findings, as determined by the Investigator, occur in any of the vital signs measurements, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

6.1.5.2 Physical and Neurological Examinations

The full physical examination will consist of the following: general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities. All physical exams will also include an assessment of the subject's height and weight.

A brief neurological examination will consist of the following: mental status, cranial nerves, nystagmus, motor system, sensory system, reflexes, coordination, gait, and station.

The subject's developmental capabilities will be assessed as a part of the neurological examination (in a manner the Investigator sees fit) during the Screening Period (Visit 1) or Visit 2 (Day 1) only, whichever visit occurs first for each respective subject.

Additional examinations may be performed at the discretion of the Investigator.

6.1.5.3 ECGs

The ECGs will be performed at the time points specified in Table 1.

Subjects should be supine for ≥5 minutes prior to the assessment.

If the first ECG is abnormal, up to an additional 2 repetitions of a specific assessment may be performed.

6.1.5.4 C-SSRS

The Columbia-Suicide Rating Scale (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. The risk of suicide will be evaluated using the C-SSRS for patients aged >=7 years. Clinical impression will be used for patients < 7 years and for patients with development impairment for whom the C-SSRS would be inappropriate. The questionnaires will be completed at the time points specified by the schedule of assessments in Table 1.

6.1.5.5 Medical/Surgical History

A complete medical/surgical history will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematological/lymphatic, allergies/drug sensitivities, past surgeries, or any other diseases or disorders.

6.1.6 Safety-related Endpoints

The safety-related endpoints are:

- Incidence, type, and severity of AEs and SAEs associated with Cannabidiol Oral Solution as an adjunctive treatment for seizures
- Changes from baseline in the previous study in vital signs
- Changes from baseline in the previous study in ECG findings
- Changes from baseline in the previous study laboratory values (hematology, chemistry, and urinalysis).

6.2 Plasma Levels

Whole blood will be obtained in a Vacutainer® containing heparin anticoagulant for the determination of the plasma levels of cannabidiol and 7-OH cannabidiol in human plasma. The sample will be obtained as indicated in Table 1 prior to daily study medication dosing on that day. Samples for plasma level assessment of cannabidiol and 7-OH cannabidiol should

be collected immediately prior to administration of the morning dose of the investigational product on indicated days.

The following information will be captured for blood sample collection in each subject's eCRF:

- Subject number and initials
- Time and date of most recent administration of the investigational product prior to the sample collected for plasma level analysis
- Time and date of each blood sample collected for plasma level analysis
- Time and date of subject's ingestion of food (i.e., the evening meal on the day prior to each study visit).

Samples for the determination of the investigational product in human plasma will be analyzed by the Sponsor, using an appropriate bioanalytical method. It is anticipated that this will include estimates of concentration and trough (steady state) concentration of cannabidiol and 7-OH cannabidiol (monthly to quarterly). For subjects taking clobazam, levels of clobazam and its major metabolite (norclobazam) will be measured if there are safety concerns.

The analytical method for human plasma will be developed and validated. All samples still within the known stability of the investigational product will be analyzed.

Exploratory plasma samples will be shipped to the Sponsor or the Sponsor-designated bioanalytical laboratory.

6.2.1 Plasma Levels-related Endpoint

The plasma level-related endpoint is trough (steady state) concentrations of Cannabidiol Oral Solution throughout approximately 48 weeks of continuous exposure or until the investigational product is successfully approved for marketing in the US (whichever occurs earlier), inclusive of the subject's treatment on their previous study.

6.3 Efficacy

6.3.1 Seizure Control

In this study, seizure frequency, duration, and severity will be assessed to monitor seizure control achieved by long-term treatment with Cannabidiol Oral Solution. Seizures will be observed and recorded using a patient reported outcome (PRO) instrument (i.e.,

subject/caregiver diaries). The exact format and version(s) of diary to be used will also be included in the eCRF. Diaries will be dispensed at Visits 7, 8, and 9 (Weeks 12, 24, and 36) and reviewed and completed pages collected (if applicable) during each visit.

For the purposes of this study, only observable seizures will be quantified in the one week prior to Visits 8, 9, and 10. All seizures should be recorded by the parent(s)/caregiver(s) and/or subject (if applicable) in the diary.

Given that continuous seizures may be observed in some subjects (i.e., multiple seizures may occur without break), it may not be possible to accurately record all seizures for these subjects. If necessary, the parent(s)/caregiver(s) or subject (if applicable) will, at a minimum, categorize the seizure frequency (for seizures others than tonic or atonic seizures) by range (i.e., diaries will record the count of seizures per day as >50 seizures/day, 20 to 50 seizures/day, 6 to 19 seizures/day, 1 to 5 seizures/day, or no seizures).

The subject and/or his/her parent(s)/caregiver(s) are responsible for completing the diary. The party who is primarily responsible will be chosen by the Investigator in consultation with the subject's parent(s)/caregiver(s). If a pediatric subject will be entering diary data, the parent(s)/caregiver(s) should provide guidance and monitor accuracy and completeness.

6.3.1.1 Subject Seizure and Dosing Diary Education

Similar to INS011-14-029 and INS011-15-054, ongoing training and re-education of the parent(s)/caregiver(s) and (if applicable) the subject will occur under the direction of the Investigator and Study Coordinator.

To this end, the Investigator and study center staff are expected to provide appropriate (refresher) training to subjects and/or their parent(s)/caregiver(s) regarding data to be collected. To satisfy the needs of all seizure-related efficacy endpoints, training will include a number of topics:

- Recognition of seizure activity
    - Such training will facilitate the counting of seizures to satisfy the primary efficacy endpoint, as well as other efficacy-related endpoints.
    - For the purposes of this study, a seizure will be defined as uncontrolled electrical activity in the brain that may produce a physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms.
- Recognition of the characteristics of relevant seizure types as described in Section 6.3.1.1.1

- Quantification of seizure severity as described in Section 6.3.1.1.3
- Quantification of seizure duration as described in Section 6.3.1.1.3

It is anticipated that training on the above topics will allow the parent(s)/caregiver(s) and subject (if applicable) to completely and accurately record seizure activity. The Investigator is responsible for ensuring that the parent(s)/caregiver(s) and subject (if applicable) are properly trained to complete the diary. Competency will be confirmed by review of diary entries with parent(s)/caregiver(s) and subject (if applicable) at each study center visit (see Table 1) so the Investigator and study center staff can monitor the quality of record-keeping.

The subject seizure and dosing diary for this study was designed to satisfy current FDA guidance regarding PROs (i.e., the Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims).

6.3.1.1.1 Seizure Type Identification

Characteristics of the seizure types to be observed and recorded for efficacy assessments (i.e., subject/caregiver diaries) include:

- Tonic: body stiffening, upward deviation of the eyes, pupil dilation, and altered respiratory patterns
- Atonic: brief loss of muscle tone and consciousness, that may result in an abrupt fall
- Myoclonic: sudden muscle jerks and including infantile spasms
- Tonic-clonic: jerking preceded by stiffening
- Clonic: repeated jerking
- Absence: lapses of awareness, sometimes with staring
- Febrile: seizure of various types (especially tonic-clonic) associated with high fever
- Focal: typically involving 1 side and/or region of the body, twitching, and grimacing
- Atypical absence: staring (as in an absence seizure), but subject may also be somewhat responsive.

These observable characteristics will be utilized to assist the parents(s)/caregiver(s) and subject (if applicable) in categorizing seizures types in the subject seizure and dosing diary. The Investigator will fully train the parents(s)/caregiver(s) and subject (if applicable) in methods to identify seizure type.

6.3.1.1.2 Seizure Severity Assessment

Subject/caregiver diaries will also be utilized to record seizure severity. Overall, seizure severity will be captured using the CGI-S as described in Section 6.3.3. This scale will be completed as noted in Table 1.

Seizure severity will be determined by the parent(s)/caregiver(s). In the subject seizure and dosing diary, the Investigators will work with the parent(s)/caregiver(s) to record an assessment of seizure severity based on the following:

- Postictal events and duration
- Occurrence of injuries
- Overall functional impairment.

The Investigator and study center staff are expected to provide appropriate training to subjects and/or the parent(s)/caregiver(s) regarding data to be collected.

6.3.1.1.3 Seizure Duration Assessment

Seizure duration will be quantified by approximate timing by the caregiver or other observer, and recorded in the subject seizure and dosing diary. The Investigator and study center staff are expected to provide appropriate training to subjects and/or their parent(s)/caregiver(s) regarding recording seizure duration.

6.3.2 Additional Information to be Recorded in Subject Seizure and Dosing Diary

The subject seizure and dosing diary will include a record of the date and time of each administration of the investigational product in the one week prior to Visits 8, 9, and 10.

6.3.3 Qualitative Assessments

In this study, the global status of each subject will be monitoring using a set of qualitative assessment tools administered at specified visits:

- CGI-I
- CGI-S
- IPES
- VABS
- C-SSRS (for subjects ≥7 years of [developmental] age).

Study center staff will be trained in the administration of these scales during the Investigator Meeting(s).

6.3.4 Efficacy-related Data to be Reported

For this study, efficacy data will be collected, analyzed, and reported, but will not be considered as study endpoints. These data include the following and will include only data collected during this study:

- Frequency, duration, and severity of seizures (i.e., seizure control)
- Parent(s)/caregiver(s) CGI-I and CGI-S
- Investigator CGI-I and CGI-S
- IPES and VABS scores
- C-SSRS

The above scales will be administered to subjects as per their chronological or developmental age as discussed in Section 3.1. Subjects enrolled from INS011-15-054 will be excluded from IPES, VABS, and C-SSRS scores evaluation.

6.4 Appropriateness of Measurements

All assessments will be performed using methods that are considered standard and appropriate.

7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the ICH Guidelines of GCP (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator and study center staff familiarity with GCP/ICH
- Investigator Meeting(s), including protocol and study systems training
- Instruction manuals for investigational product, IVRS, EDC, and any other systems included in study operation
- Central laboratories for clinical laboratory parameters and ECGs
- Study Center Initiation Visit
- Early study center visit following enrollment of the first subject
- Routine study center monitoring
- Ongoing study center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report (CSR).

In addition, the Sponsor and/or designee may conduct periodic audits of the study processes, including, but not limited to the study center, study center visits, central laboratories, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

7.1 Monitoring

The Sponsor may engage the services of a contract research organization (CRO) to perform all monitoring functions within this clinical study. Monitoring will occur according to GCP and the designee's monitors will work in accordance with their SOPs and have the same rights and responsibilities as monitors from the Sponsor. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of the study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study center. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while subjects are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, all entries in the eCRFs will be compared with the original source documents (source data verification).

7.2 Data Management/Coding

Data generated within this study will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor or designee.

A Code of Federal Regulations (CFR) Title 21, Part 11-compliant EDC system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. The eCRFs will be produced by the Sponsor or designee for each subject. Where eCRFs are not possible, the source data will be captured on paper.

Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon

as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all plasma level and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives investigational product, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

The eCRFs will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time

stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Concomitant diseases/medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization's Drug-Dictionary (WHO-DD).

7.3 Quality Assurance Audit

The study center, the study database, and study documentation may be subject to quality assurance audits during the course of the study by the Sponsor or a designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded for data queries and all required reports according to any instructions provided.

8.0 STATISTICS

8.1 Determination of Sample Size

The sample size will be determined by the number of subjects who are eligible to and elect to rollover from INS011-14-029 or INS011-15-054. These studies would contribute up to a maximum of 60 and 20 subjects respectively.

8.2 General Statistical Considerations

8.2.1 Statistical Methods and Analysis Plan

This section describes the planned statistical analyses in general terms. A complete description of the methodology will be specified in the SAP. Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

8.2.2 General

Since this is an extension study of INS011-14-029 and INS011-15-054 data for INS011-14-030 will be presented for the extension period only (i.e., not for the entire period spanning INS011-14-029 and INS011-15-054 and INS011-14-030 studies).

Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum).

Baseline for this study will be the same as that defined in protocols INS011-14-029 and INS011-15-054, respectively. Additionally, all data from this study will also be compared to the intra-study baseline (data from the subject's first visit [i.e., Visit 1 [Screening] or Visit 2 [Day 1]). For assessments that were not completed in INS011-14-029 (i.e., IPES and VABS), the only baseline will be data collected at Visit 2 (Day 1) of INS011-14-030. (Data from subjects enrolling through INS011-15-054 may be excluded from the analysis)

Data collected at unscheduled time points will not be summarized at the unscheduled time points.

Data will be presented for each dose (10, 20, and 40 mg/kg/day) and for all doses combined together (overall), corresponding to the dose at which subject will initiate this study (as described in Section 4.1). When appropriate, raw data will be presented by visit (Visit 1

[Screening], Visit 2 [Day 1], Visit 3 [Week 1], Visit 4 [Week 2], then monthly for 3 months, and then quarterly thereafter).

No statistical hypothesis testing is planned for this study.

A detailed SAP will be finalized prior to database lock.

8.2.3 Data to be Analyzed

The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings, and figures (TLFs) will be described in the SAP prepared by the Sponsor or by a designee and approved by the Sponsor before database lock.

8.3 Statistical Considerations

8.3.1 Subject Population for Analysis

The analysis population will be the Safety Population, which will include all subjects who receive ≥1 dose of the investigational product. In the event that a subject receives treatment other than that specified in the protocol, safety analyses will be conducted according to the treatment the subject actually received.

All safety-related endpoints and efficacy-related data will be analyzed using the Safety Population.

8.3.2 Subject Disposition

The number of subjects who receive each dose and the duration of exposure will be summarized for the Safety Population.

Prior and concomitant therapies will be listed. The frequency and percentage of subjects who use prior or concomitant medication will be summarized by preferred term (PT), utilizing WHO-DD definition and treatment regimen for each dose and overall. Concomitant medications will also be checked for protocol deviations.

Subjects who take prohibited concomitant medications will be noted in the summary of protocol deviations.

8.3.3 Demography and Other Baseline Data

Demographic data and subject characteristics will be listed and summarized by dose and for all subjects using descriptive statistics (mean, number, SD, median, minimum, and maximum values for continuous variables and counts and percentages for categorical variables).

Past and current medical history will be summarized by dose and overall using the system organ class (SOC) as coded using the MedDRA coding dictionary. If both a past and current (ongoing) medical condition record are indicated for a condition, the condition will be presented under current medical conditions only.

8.3.4 Safety Analysis

The assessment of safety will be based on the analyses of AEs, vital signs, 12-lead ECG, and clinical laboratory evaluations. All safety analyses will be performed on the Safety Population. Safety endpoints are described in Section 6.1.6.

8.3.4.1 AEs

The TEAEs are defined as AEs that first occur or worsen in severity after the first administration of the investigational product. Such AEs will be coded using the MedDRA coding dictionary and will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each SOC, and having each individual AE as reported by PT. Furthermore, a summary for SAEs and summaries by severity and relationship to the investigational product will be presented by dose and overall. The most frequent (5%) AEs and drug related AEs will also be provided.

All percentages will be based on the number of subjects in the Safety Population.

In the summaries, AEs will be counted only once per subject. If a subject reports the same AE more than once, it will be counted with its worst severity and closest relationship to investigational product. Only those AEs that begin between start and end of study will be summarized.

The AEs will also be listed by subject and dose.

Subject death due to any cause and subjects with AEs leading to investigational product discontinuation will be listed and summarized by dose and overall.

The proportion of subjects that discontinue investigational product or experience dose interruption due to treatment emergent AEs will be summarized by dose and for all subjects.

8.3.4.2 Clinical Laboratory Evaluations

Proportions of subjects who develop clinical laboratory result abnormalities of interest will be summarized by dose and overall.

Summary statistics (mean, median, SD, minimum value, and maximum value) over time will be presented by dose and overall at each visit for the continuous laboratory parameters. Descriptive statistics of changes from baseline by visit will also be presented for each dose and for all subjects.

A frequency table of results of categorical laboratory parameters will be produced. Furthermore, laboratory abnormalities will be analyzed by shift tables where each subject will be counted only once with the worst grade in the summary tables.

All laboratory data will be listed with abnormal values flagged.

8.3.4.3 Vital Sign Measurements

Vital signs (including the raw data and the changes from baseline) will be listed and summarized over time by visit for each dose and overall. Notable values and changes will be tabulated.

8.3.4.4 ECG Evaluations

The ECG evaluations will be summarized by visit for each dose and overall.

Descriptive statistics (number, mean, SD, median, minimum value, and maximum value) of the continuous ECG parameters will be presented at each assessment visit for both raw data and change from baseline data, respectively, for each dose and overall. Frequency counts will be presented by visit for both change and absolute values for each dose and overall.

Individual listings presenting subjects with flags will be created for both change and absolute values.

8.3.5 Analysis of Cannabidiol and 7-OH Metabolite Concentrations

Cannabidiol and 7-OH cannabidiol concentrations will be measured at baseline, after the first dose, and periodically thereafter (see Table 1 and Section 6.2). A descriptive summary of observed blood concentration (number, mean, SD, minimum value, and maximum value) will be displayed at each interval.

The plasma concentration data from this study may be combined with data collected in INS011-14-029 and INS011-15-054 for population PK model development. An independent SAP will detail this analysis.

8.3.6 Efficacy Analysis

Although these data do not represent endpoints for this long-term safety study (see Section 6.3), they will be analyzed and reported:

- Frequency, duration, and severity of seizures (i.e., seizure control)
- Parent(s)/caregiver(s) CGI-I and CGI-S
- Investigator CGI-I and CGI-S
- IPES and VABS scores
- C-SSRS.

The above scales will be administered to subjects as per their chronological or developmental age as discussed in Section 3.1. Subjects enrolled from INS011-15-054 will be excluded from IPES, VABS, and C-SSRS scores evaluation.

8.3.6.1 Seizure-related Data

All seizure-related parameters (in terms of raw data and percentage change from baseline) will be listed and summarized by dose and for all subjects using descriptive statistics (mean, number, SD, median, minimum, and maximum values for continuous variables).

No statistical inferential procedures will be performed.

8.3.6.2 Qualitative Subject Status Assessments

All qualitative subject status assessments (CGI-I, CGI-S, IPES, VABS, and C-SSRS related parameters) will be listed and summarized by dose and overall using descriptive statistics (mean, number, SD, median, minimum, and maximum values for continuous variables).

No statistical inferential procedures will be performed.

8.4 Interim analysis

An interim analysis may be conducted if deemed necessary.

8.5 Handling of Missing Values

In general, for all analyses, observed values will be used and no imputation will be made for missing values. For specific endpoints and special instances, details for handling missing values will be described in the SAP.

9.0 ETHICS

9.1 Institutional Review Board

An IRB/IEC must approve the final protocol, including the final version of the ICF and Assent Form and any other written information and/or materials to be provided to the subjects. The Investigator will provide the Sponsor or a designee with documentation of IRB approval of the protocol and informed consent before the study may begin at the study center. The Investigator should submit the written approval to the Sponsor or designee before enrolment of any subject into the study.

The Sponsor or a representative should approve any modifications to the ICF that are needed to meet local requirements.

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

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

9.2 Ethical Conduct of the Study

This study will be conducted and informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), the applicable guidelines for GCP (Committee for Medicinal Products for Human Use [CHMP]/ICH/135/95), or the applicable drug, and data protection laws and regulations of the country where the study will be conducted.

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

9.3 Subject Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the ICF and assent form (if applicable) prior to the performance of any protocol procedures and prior to the administration of study medication. The Investigator will provide each subject with a copy of the signed and dated ICF.

9.3.1 Subject Assent Guidance

This study may enroll children as young as 1 year of age (see Section 3.4.1). The IRB/IEC must determine, to the extent required by 45 CFR §46.116, that adequate provisions are made for soliciting the assent of pediatric subjects (when the IRB/IEC judges that they are capable of providing assent), as well as the permission of the parents (45 CFR §46.408). Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research (45 CFR §46.402(c)). Local and regional/state regulations will also be addressed as applicable.

If the IRB/IEC determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted regarding assent, or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children, and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB/IEC determines that the subjects are capable of assenting, the IRB/IEC may still waive the assent requirement under certain circumstances in accord with 45 CFR §46.116 and 45 CFR §46.408(a).

The IRB/IEC and local regulations will determine the age at which assent of subjects in this study will not be required. Informed consent from all parent(s)/caregiver(s) will be required.

10.0 STUDY ADMINISTRATION

10.1 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation).

The US FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational product, including eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator for 15 years after the last marketing application approval in an ICH region or after at least 15 years have elapsed since formal discontinuation of clinical development of the investigational will notify the Investigator of these events.

Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records. No records should be disposed of without the written approval of the Sponsor.

10.2 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow the Sponsor, its designee, study monitors, and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate.

10.3 Investigator Information

10.3.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (1997); the US CFR Title 21 parts 50, 56, and 312; and European Legislation; and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator agrees to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

10.3.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or its representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any center where the Investigator has not signed the protocol.

10.3.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

10.4 Financing and Insurance

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of the insurance will be kept in the study files.

Appendix 1: Signature of Investigator

PROTOCOL TITLE: A multicenter, open-label, flexible dose study to assess the long-term safety of pharmaceutical Cannabidiol Oral Solution as an adjunctive treatment for pediatric subjects with a treatment-resistant seizure disorder who complete INS011-14-029, or Part A in INS011-15-054

PROTOCOL NO: INS011-14-030, Amendment 5

This protocol is a confidential communication of Insys Development Company, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Insys Development Company, Inc.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to Insys Development Company, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

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9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

The original protocol dated 27 October 2014 was amended four times. Protocol Amendments 1 and two were instituted before the first subject was enrolled. Copies of the protocol and protocol amendments are provided in Appendix 16.1.1. Brief summaries of the nonadministrative changes are outlined below.

9.8.1.1 Protocol Amendment 1

Amendment 1 dated 11 December 2014 implemented the following changes:

- Updated planned number of subjects to remove eight additional subjects from INS011-14-029;
- Modified exclusion criteria as follows:
  - Clarified exclusionary anoxic episodes;
  - Removed exclusion based on neurometabolic, neurodegenerative, or progressive neuro-oncological disease;
  - Added exclusion based on suicidal ideation.
- Retitled the Safety Review Committee as a Medical and Safety Data Review;
- Updated the schedule of events to reflect changes to the protocol;
- Clarified that all study procedures performed during scheduled study visits should occur prior to administration of study drug;
- Changed Adverse Event guidelines from the Common Terminology Criteria for Adverse Events to the MedDRA;
- Added valproic acid and phenobarbital to Appendix 2: CYP3A4-Related Prohibited Medications;
- Added all scales to Appendix 4: Scales.

9.8.1.2 Protocol Amendment 2

Amendment 2 dated 07 August 2015 implemented the following changes:

- Clarified study duration to include provision to retain subjects on-study until marketing approval in the US;

- Updated information regarding formulation of the investigational product;
- Updated the schedule of assessments as follows:
  - Added a review of subject eligibility in the event of a prolonged (> 14-day) gap in administration of the investigational product;
  - Removed a subset of qualitative assessments;
  - Updated period in which subject diary data was collected.

9.8.1.3 Protocol Amendment 3

Amendment 3 dated 08 April 2016 implemented the following changes:

- Added Australia as a clinical conduct country;
- Updated inclusion criterion #3 to allow the Investigator to judge medical stability of subjects;
- Updated inclusion criterion #4 to note that special monitoring was required for subjects taking drugs metabolized by CYP enzymes (see Section 9.4.7.2);
- Updated inclusion criteria #5 and #6 language regarding required contraception;
- Removed eligibility criteria that excluded subjects who were taking concomitant medications that are strong CYP3A4 inhibitors or inducers or CYP3A4-sensitive substrates with a narrow therapeutic index or who had sleep apnea;
- Updated exclusion criterion #6, schedule of assessments, and throughout protocol to note that C-SSSR was to be utilized for appropriate subjects (from a developmental age perspective);
- Added that clinical impression of suicidality was to be utilized in place of the C-SSRS for subjects < 7 years of age;
- Updated that the dose of the investigational product could be increased to a maximum dose of 40 mg/kg/day;
- Updated the schedule of assessments to include collection of plasma level samples for Visit 5, Visit 6, and Visit 7;
- Clarified that dose of the investigational product may be adjusted based on changes in subject weight;
- Clarified that background AEDs, ketogenic diet, and VNS settings could have been adjusted as needed for seizure control and tolerability as per the Investigator's judgement;

- Clarified that date and time of administration of the investigational product, and the frequency, duration and severity of seizures were only required to be recorded for one week prior to Visit 8, Visit 9, and Visit 10;
- Removed the following as prohibited medications and foods:
  - Medication (s) that are strong CYP3A4 inhibitors or inducers or CYP3A4-sensitive substrates with a narrow therapeutic index;
  - Corticotrophins;
  - Systemic steroid therapy (excluding inhaled medication for asthma treatment) or any other daily medications known to exacerbate epilepsy;
  - Felbamate (if used for at least six months);
  - Consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges.
- Updated to allow for new AEDs to be added to background therapy;
- Clarified that developmental capability, rather than chronological age, were to be used to determine whether the subject completed the CGI-S for themselves;
- Updated identifying description of myoclonic seizures.

9.8.1.4 Protocol Amendment 4

Amendment 4 dated 05 October 2016 implemented the following changes:

- Removed Australia as a clinical conduct country;
- Allowed subjects from INS011-15-054 to rollover into this study after completion of Part A (Visit 6);
- Removed all references to INS011-14-024 and INS011-14-025;
- Reduced the number of study centers from 45 to 10;
- Allowed study centers to collect diet information, including time of closest meal to administration of the investigational product and use of ketogenic diet;
- Added recommendations regarding administration of the investigational product with regards to timing of meals;
- Reduced sample size from 232 to 80 subjects;

- Updated exclusion criterion #4 to allow Investigators to enroll subjects with clinically significant abnormal lab values that the Investigator judged acceptable and to have no impact on subject safety;
- Allowed Investigators to adjust subject dose at any time as long as the maximum dose did not exceed 40 mg/kg/day;
- Excluded subjects enrolling from INS011-15-054 from completing IPES, VABS, and C-SSRS evaluations;
- Restricted conduct of the VABS assessment to Visit 2 and Visit 10;
- Added guidance regarding the circumstances under which a seizure was considered an AE;
- Removed the following as prohibited medications for subjects diagnosed with DS:
  - Carbamazepine;
  - Eslicarbazepine;
  - Oxcarbazepine;
  - Lamotrigine;
  - Phenytoin.

9.8.1.5 Administrative Change 1

Administrative Change 1 dated 01 November 2016 removed all references to adult subjects or subjects > 18 years were removed from the protocol.

9.8.1.6 Protocol Amendment 5

Amendment 5 dated 06 March 2017 implemented the following change:

- Added a description of dose tapering procedures for subjects who were not continuing to receive the investigational product under an Investigator IND Expanded Access Program;
- Specified that dose tapering should be planned in advance to allow sufficient time to complete the taper prior to Visit 10 at 48 weeks (±10 days).

9.8.2 Changes in the Planned Analyses

Changes that were made to the planned analyses after the finalization of the SAP were as follows:

- Given that an Investigator could have chosen to down-titrate or up-titrate subjects to any dose, results were not analyzed and presented "by dose and overall" as was stated in the protocol. On 13 October 2016, it was decided that summaries should only be presented by age category and overall as described in Sections 9 to 17 of the SAP (Appendix 16.1.9).