CLINICAL TRIAL PROTOCOL

A Multicenter, Open-Label Study to Assess the Long-Term Safety of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Patients with Prader-Willi Syndrome

Protocol Number: INS011-17-115
Final Protocol Date: 27 Feb 2018
Version: 1.0
Investigational Product: Cannabidiol Oral Solution
IND Number: IND 136,374

ClinicalTrials.gov ID: NCT03458416

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Investigational Product:	Cannabidiol Oral Solution
IND Number:	136,374
Sponsor:	Insys Development Company, Inc. 1333 South Spectrum Blvd, Suite 100 Chandler, AZ 85286
Medical Monitor:	PPD DO Insys Development Company, Inc. Sr. Director, Clinical Development/Medical Affairs Phone: PPD Fax: PPD

Confidentiality Statement

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

PROTOCOL APPROVAL PAGE

A Multicenter, Open-Label Study to Assess the Long-Term Safety of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Patients with Prader-Willi Syndrome

Protocol Approved by:

PPD

Sr. Director, Clinical Operations

Insys Development Company, Inc.

PPD

Date: 27 Feb 2018

PPD

PPD Regulatory Affairs

Insys Development Company, Inc.

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Date: 27 Feb 2018

PPD DO

Sr. Director, Clinical Development/Medical Affairs

Insys Development Company, Inc.

PPD

Date: 27 Feb 2018

PROTOCOL SYNOPSIS

Name of Sponsor/Company:

Insys Development Company, Inc.

Name of Investigational Product:

Cannabidiol Oral Solution

Name of Active Ingredient:

Cannabidiol

Title of Study:

A Multicenter, Open-Label Study to Assess the Long-Term Safety of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Patients with Prader-Willi Syndrome

Study center(s): Approximately 10 sites in the US.

Phase of development: Phase 2

Objective:

The objective of this study is to assess the long-term safety and tolerability of Cannabidiol Oral Solution (CBD) in patients with Prader-Willi Syndrome.

Methodology:

This is a multicenter, open-label study designed to assess long-term safety and tolerability of CBD in patients with Prader-Willi Syndrome. Patients must have completed INS011-16-085 to be eligible.

The Investigator will ensure that the patients legal representative [parent(s)/caregiver(s)] will receive a copy of the informed consent form for review and provide full informed consent prior to study participation. Patients may enroll in this long-term safety study (INS011-17-115) after completing INS011-16-085 Visit 10 (Study Completion) to avoid interruption of the investigational product. Patients will have up to 2 weeks to enroll in INS011-17-115.

Patients will receive CBD treatment for approximately 48 weeks. Total daily doses ranging from 20 mg/kg/day to 40 mg/kg/day will be administered with standard meal. If any participant does not enroll within the 2 week window, that patient will not be eligible to enroll into the study.

The study will consist of a Safety Period (48±2 weeks), Taper Period (6±3 days), and a Follow-up Period (30±5 days). Treatment visits will be scheduled monthly for the first 3 months and then quarterly over the remaining 9 months. All patients will complete a Visit 7 (End of Study) or Early Withdrawal Visit regardless of when they stop treatment/complete the study. A Follow-Up telephone call (Visit 9) will occur 30 days after the end of either the End of Study (Visit 7) or Early Withdrawal.

Patients will be dosed approximately every 12 hours with food to help ensure consistent plasma levels are achieved. Patients will be dosed for 48 weeks during which the investigator will assess safety and tolerability.

Study Assessments

At Visit 1 (Day 1) and each monthly and quarterly visit, the following assessments will be completed:

- Review of concomitant medications.
- Review of vital signs.
- Review clinical labs.
- Urinanalysis (Visit 1 only).
- Urine pregnancy screening for post-menarchal females.
- Columbia-Suicide Severity Rating Scale (C-SSRS).
- Dispensing CBD.
- Drug accountability.
- Review adverse events (AEs).
- 12-lead ECG
- Physical examination.
- Weight.
- Urine drug screen.
- Urine pregnancy screen for post-menarchal females

At End of Study (Visit 7) or Early Withdrawal, the following assessments will be completed:

- Review of concomitant medications.
- Review clinical labs
- 12-lead ECG.
- Review AEs.
- Review of vital signs.
- Drug accountability.
- Urine drug screen.
- Urinalysis.
- Urine pregnancy screen for post-menarchal females.
- Physical examination.
- Weight.
- Dispensing CBD.
- Columbia-Suicide Severity Rating Scale (C-SSRS).
- Hyperphagia Questionnaire for Clinical Trial (HQ-CT)

At Taper Period (Visit 8), the following will be completed:

- Collect CBD.
- Review AEs.

At Follow-Up (phone call only), the following assesments will be completed:

- Review of concomitant medications.
- Review AEs.

Taper Period

At the end of the Long-Term Safety study, patients will be tapered off of CBD. The following tapering scheme will be utilizied: 40 mg/kg/day will be reduced to 30 mg/kg/day for three days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for three days, then discontinued; 30 mg/kg/day will be reduced to 20 mg/kg/day for three days, then discontinued. This can be modified by the investigator based upon the patient's response.

Tapering will occur under the following circumstances:

- Patient completes Visit 7 (End of Study). Patient will begin tapering the day after Visit 7.
- Patient withdraws early. Patient will begin tapering the day after they decide to withraw from the trial.

Follow-Up Period

A Follow-up telephone call will occur 30 days after the End of Study (Visit 7) or Early Withdrawal AEs and record concomitant medications.

Number of patients (planned):

Approximatley 66 patients who completed INS011-16-085 will be enrolled in the study.

Diagnosis and main criteria for inclusion:

Inclusion criteria

1. Completed activities up to and including Visit 10 (Study Completion) of INS011-16-085.
2. Patient and/or parent(s)/caregiver(s) fully comprehend the informed consent form (ICF) and assent form, understand all study procedures, and can communicate satisfactorily with the investigator and study coordinator, in accordance with applicable laws, regulations, and local requirements.
3. If female, is either not of childbearing potential (defined as premenarchal or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing one of the following medically acceptable methods of birth control:
   a. Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives for a minimum of 1 full cycle (based on the patient's usual menstrual cycle period) before study drug administration.
   b. Total abstinence from sexual intercourse since the last menses before study drug administration.
   c. Intrauterine device.
   d. Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream). Growth hormone treatment will be permitted if doses have been stable for at least 1 month prior to screening.

4. Psychotropic treatment will be permitted if the subject has been on a stable dose during the INS011-16-085 and does not anticipate a dose change during the course of the study.
5. Growth hormone treatment will be permitted if the subject has been on a stable dose during INS01-16-085.
6. Any other treatment including thyroid hormones should be stable prior to entering the INS011-17-113 study.
7. In the opinion of the investigator, the parent(s)/caregiver(s) is (are) willing and able to comply with the study procedures and visit schedules, including venipuncture, and the visit schedules.

Exclusion criteria

1. Patient or parent(s)/caregiver(s) have commitments during the study duration that would interfere with attending all study visits.
2. Experienced an anoxic episode related to study drug requiring resuscitation during the previous study.
3. Uncontrolled Type I and Type II Diabetes.
4. Developed an adverse event thought to be related to CBD in the previous study and the investigator determines that continuing treatment with CBD would not be in the best interest of the patient.
5. History of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or other condition which would jeopardize safety or impact validity of results (per investigator).
6. Currently taking felbamate.
7. Compromised respiratory function or severe respiratory insufficiency.
8. Pregnant or lactating female..
9. In the opinion of the investigator, the patient is unsuitable in any other way to participate in this study.

Investigational product, dosage and mode of administration:

Cannabidiol Oral Solution, 20 mg/kg/day, 30 mg/kg/day, and 40 mg/kg/day, divided into twice daily doses with standard meal, manufactured for and supplied by Insys Development Company, Inc.

Duration of treatment:

The maximum duration of the study from Visit 1 (Day 1) to follow-up call will be approximately 54 weeks (±3 weeks).

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Safety Endpoints

- Incidence, type, and severity of AEs and serious adverse events (SAEs) associated with Cannabidiol Oral Solution (i.e., treatment-emergent adverse events [TEAEs]).
- Changes from baseline in vital signs, ECG findings, and laboratory values (hematology, chemistry, and urinalysis).
- Change from baseline in weight.

Exploratory Efficacy Endpoint

- Change in total score of the HQ-CT from Baseline to Study Completion/Early Withdrawal.

Baseline is defined as Visit 10 of INS011-16-085.

Statistical Methods:

Safety Analysis

All safety assessments, including AEs, clinical laboratory evaluations, vital signs, 12-lead ECGs, and physical examination (including weight) will be listed for each visit. When appropriate, they will be summarized with descriptive statistics by age and dose cohort. The Medical Dictionary for Regulatory Activities (MedDRA; Version 20.0 or higher) will be used to classify all adverse events with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group.

- Clinical laboratory findings and vital signs will be summarized for all patients for observed values and change from baseline. Shifts from baseline to outside normal range criteria will also be presented for all patients.
- Weight will be listed and summarized for all patients for observed values and change from baseline. Shifts from baseline to outside normal range criteria will also be presented for all patients.
- Results of physical examinations conducted throughout the study will be presented in listings and summarized descriptively. Shifts from baseline according to normal and abnormal criteria will also be presented for all patients.
- Concomitant medications will be reported in the data listings.
- Statistical analyses will be performed using SAS® (Version 9.3 or higher, SAS Institute Inc.) or R (Version 3.3 or higher, Roswell Park Cancer Institute).

Missing Data

There will be no imputation of the missing values. All assessments will be conducted based on all the observed data.

Table 1: Schedule of Events

ASSESSMENTS	SAFETY PERIOD					TAPER PERIOD	FOLLOW-UP PERIOD[g]
Visit Number	**1[a]**	**2, 3, 4 (monthly)**	**5, 6 (quarterly)**	**7 (End of Study)**	**Early Withdrawal**	**8**	**9 (Phone Call)**
Study Time Points	**Day 1**	**Weeks 4, 8, 12**	**Weeks 24, 36**	**Week 48**		**0-6 Days**	**30 Days After EOS**
Visit Window (Days)	± 5	± 5	± 5	± 3		± 3	± 5
Informed consent [**]	X						
Review of inclusion/exclusion criteria [**]	X						
C-SSRS	X			X	X		
Review concomitant medications	X	X	X	X	X	X	X
Vital signs[b]	X	X	X	X	X		
Clinical labs[c]	X	X	X	X	X		
12-lead ECG	X	X	X	X	X		
Urinalysis	X			X	X		
Urine pregnancy screen for post-menarchal females	X			X	X		
Urine drug screen	X			X	X		
Physical examination[d]	X	X	X	X	X		
Hyperphagia Questionnaire for Clinical Trial (HQ-CT)				X	X		
Dosing with Cannabidiol Oral Solution	X	X	X	X	X[e]	X[e]	
Drug accountability	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X

ASSESSMENTS	SAFETY PERIOD					TAPER PERIOD	FOLLOW-UP PERIOD[g]
Visit Number	**1[a]**	**2, 3, 4 (monthly)**	**5, 6 (quarterly)**	**7 (End of Study)**	**Early Withdrawal**	**8**	**9 (Phone Call)**
Study Time Points	**Day 1**	**Weeks 4, 8, 12**	**Weeks 24, 36**	**Week 48**		**0-6 Days**	**30 Days After EOS**
Visit Window (Days)	± 5	± 5	± 5	± 3		± 3	± 5
End of Study				X	X[f]		

[**] To be completed prior to enrollment into LTS, specifically within the 2-week period that is allotted post completion of Visit 10 (Study Completion) of INS011-16-085.
[a] For patients who enroll within the first 2 weeks after completion of Visit 10 (Study Completion) of INS011-16-085 protocol.
[b] Vital signs will be taken after a 5-minute seated rest.
[c] If the total bilirubin laboratory value is abnormal, direct bilirubin will be drawn.
[d] The physical examination will include weight, and evaluation of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities.
[e] Following the Safety Period or if the patient withdraws early, the patient will enter a Taper Period. Patients will be tapered off of Cannabidiol Oral Solution as follows: 40 mg/kg/day will be reduced to 30 mg/kg/day for three days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for three days, then discontinued; 30 mg/kg/day will be reduced to 20 mg/kg/day for three days, then discontinued. This can be modified by the investigator based upon the patient's response.
[f] If the patient withdraws prematurely from the Safety Period, all Visit 7 (End of Study) procedures should be conducted. Site staff will follow up with the patient 4 weeks after completion of treatment via the telephone to collect information regarding AEs and concomitant medications.
[g] Follow-up Period Visit 9 will be a phone call.
AE = adverse event.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
5-HT_{1a}	5-hydroxytryptamine 1a
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC_{0-t}	area under the plasma concentration-time curve
AUC_{0-tau}	area under the plasma concentration-time curve to the end of the dosing period
AUC_{inf}	area under the plasma concentration-time curve extrapolated to infinity
BMI	body mass index
BUN	blood urea nitrogen
CB1	cannabinoid receptor 1
CB2	cannabinoid receptor 2
CBD	cannabidiol
CBN	cannabinol
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
CNS	central nervous system
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450 enzymes
CYP1A1	cytochrome P450 1A1
CYP2C19	cytochrome P450 2C19
CYP2C9	cytochrome P450 2C9
CYP2D6	cytochrome P450 2D6

CYP3A4	Cytochrome P450 3A4
CYP3A5	Cytochrome P450 3A5
CV%	coefficient of variation
DEA	Drug Enforcement Administration
ECG	electrocardiogram
EDC	electronic data capture
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL-2	interleukin-2
i.p.	intraperitoneal
IP	investigational product
IRB	Institutional Review Board
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MCT	medium chain triglycerides
OH	hydroxy
PK	pharmacokinetic(s)
pKa	acid dissociation constant
PWS	Prader-Willi Syndrome
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
Δ^9-THC	Δ^9-tetrahydrocannabinol

THC	tetrahydrocannabinol
THCV	tetrahydrocannabivarin
ULN	upper limit of normal
US	United States

1. INTRODUCTION

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

There is evidence that CBD may be effective in anxiety, epilepsy, chemotherapy-induced peripheral neuropathy, glioblastoma, addiction and drug dependency, post-traumatic stress disorder, weight-loss, and appetite regulation. CBD's effects on appetite, weight regulation, and anxiety are of interest to patients with Prader-Willi Syndrome (PWS), the focus of this investigation.

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

1.1. Cannabidiol

The Cannabidiol is the second most abundant cannabinoid found in the cannabis plant and is highly physiologically relevant without the psychoactive sequelae (Pertwee, 2008). In contrast, Δ^9-tetrahydrocannabinol (Δ^9-THC) is the most prevalent and principal psychoactive constituent of cannabis (Pertwee, 2008).

Insys Development Company, Inc. (hereafter referred to as the Sponsor) manufactures a synthetic pharmaceutical grade CBD drug substance. It is manufactured in a 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). The active pharmaceutical ingredient is ≥99.5% pure (Sponsor internal analysis), can be consistently produced without the concern for contaminants of other cannabinoids, is formulated with medium chain triglycerides (MCT) without alcohol specifically for pediatric use, and will provide CBD to responsibly investigate the treatment of Prader-Willi Syndrome (PWS).

Cannabis was extensively used as a medicine throughout the developed world in the 19th century. However, interest as a medicine declined as cannabis became the most widely used illicit recreational drug in the 20th century (Robson, 2014). Since the isolation and elucidation of the structure of the main active constituent of cannabis, THC, (Gaoni and Mechoulam, 1964) a large number of published articles have investigated its chemistry, biochemistry, pharmacology, and clinical effects. The effects of cannabis are not due to THC alone. At least one constituent, CBD, was found to have significant pharmacological effects on its own, some of which may modify the metabolism and effects of THC (Karniol at al., 1974; Jaeger et al., 1996).

The endogenous endocannabioid system was first described in the 1990's as the primary targets of THC were sought (Mechoulam and Parker, 2013). Studies in animals have demonstrated an effect of CBD on appetite, food consumption, and reward system, from sugar intake felt to interact with the endogenous endocannabinoid system's effects on these activities (Silveira Filho and Tufik, 1981; Parsons and Hurd, 2015; Edwards and Abizaid, 2016). In addition, CBD has been observed to have anxiolytic and anti-psychotic properties, two comorbidities that are highly prevalent in patients with PWS (Whitman and Accardo, 1987; Crippa et al., 2010). Taken together, CBD may have an impact on both the hyperphagia-related disorders and subsequent obesity related to PWS.

1.1.1. Mechanism of Action

The mode of action of CBD is not fully understood. While THC is a strong agonist of the endogenous cannabinoid receptors 1 (CB1) and 2 (CB2), CBD has only a low-affinity for these receptors and is believed to be a non-competitive antagonist/inverse agonist to them both (Pertwee, 2008; McPartland, 2015; Laprairie et al., 2015). Instead, CBD has been shown to have activities at several other biologically relevant receptors in the brain. For instance, it stimulates the vanilloid receptor type 1 (Bisogno et al., 2001) and modulates, without antagonism, both μ- and δ-opioid receptors (Kathmann et al., 2006). In addition, CBD has been shown to effect bidirectional regulation of intracellular calcium homeostasis via the mitochondrial sodium/calcium exchanger (Ryan et al., 2009), have agonistic properties at 5-hydroxytryptamine 1a (5-HT_{1a}) receptors (Russo et al., 2005), and enhancing endogenous adenosine levels in the central nervous system (CNS) by reducing adenosine re-uptake leading to increased activity at the adenosine A2a receptor (Carrier et al., 2006; Jones et al., 2012).

These activities have translated to demonstration of anxiolytic effects in animals (Campos et al., 2013; Gomes et al., 2013) through activation of the 5-HT_{1a} receptors and followed with supportive observations in some human studies (Bergamaschi et al., 2011a; Crippa et al., 2011; Almeida et al., 2013). In addition, several investigations have outlined how CBD can affect the endogenous cholinergic-dopaminergic reward system suggested by decreases in cue-craving and increase in threshold for opioid self-administration (Parsons and Hurd, 2015; Prud'homme et al., 2015).

1.1.2. Metabolism and Potential Drug Interactions

The major biotransformation pathway for CBD is similar to that of other cannabinoids and mediated by hydroxylation by cytochrome P450 (CYP) proteins (Harvey et al., 1991). Cannabidiol is metabolized primarily in the liver by CYP3A4 and to a lesser extent by CYP2C19.

Its interactions with human drug metabolizing enzymes (as a substrate, inhibitor, or inducer) were recently reviewed (Stout and Cimino, 2014; Bergamaschi et al, 2011b). Specifically, CBD inhibits CYP3A4, CYP3A5, CYP2D6, and CYP1A1 in vitro (Johannessen and Landmark, 2010; Yamaori et al., 2010, 2011a, 2011b;). It also appears to inhibit CYP2C9 (Yamaori et al., 2012) and the transport protein P-glycoprotein (Holland et al., 2006; Zhu et al., 2006).

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

1.2. Nonclinical Experience

1.2.1. Safety

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

1.2.2. Efficacy

There are no prior clinical studies investigating the potential efficacy of cannabidiol in patients with Prader-Willi Syndrome. Please refer to Section 1.4 for review of potential clinical efficacy of cannabidiol from studies in different patient populations. The following is a review of non-clinical data on the use of cannabidiol on food and water intake in animals.

Eight preclinical studies examined the effect of CBD on food and water intake and/or weight gain. However, the results were often conflicting based on the dose, dosing regimen, endpoints and analyses conducted and suggest a lack of acute effect following starvation, but do suggest a sustained effect against hyperphagia-related food intake.

1.2.2.1. Single Dose Regimens

Sofia and Knobloch (1976) looked at the effect of a single dose of CBD (50 mg/kg) given to rats intraperitoneally (i.p.) on food and water intake when food plus water, food plus 5% sucrose, or food + 20% sucrose was given. They followed the animals out for 6 days after the injections. They found that CBD, as well as THC and cannabinol (CBN), led to decreased food intake which was maximal the first day and returned to normal by the 5th day. They also noted that the effect was greater for food than for the sucrose solutions. They concluded that CBD led to a preference for sweet calories and that CBD led to decreased intake. This effect decreased daily until it was no longer present, approximately 3-5 days after treatment.

Silveira Filho and Tufik (1981) noted that intake of food by albino rats was decreased after treatment with 30 mg/kg CBD compared with control rats.

Riedel et al. (2009) studied the effects of a synthetic CB1 antagonist, a phytocannabinoid (tetrahydrocannabivarin [THCV]) that acts as a CB1 antagonist, an extract rich in THCV, CBD alone, and a combination of the extract with CBD in both a single-dose regimen as well as a multiple-dose regimen (over 4 days). In the single dose regimen, mice were administered the above in either a fasted state (maximum 24 hours) or a non-fasted state after which they were allowed free access to food. As expected, the CB1 antagonists led to a decrease in food uptake and weight loss on the day post treatment. An extract rich in THCV did not result in a decline in weight that was thought to be due to the small amounts of THC present. While CBD alone at a low dose of 10 mg/kg induced a small although non-significant reduction in weight gain, in combination with the THCV-rich extract gave a significant suppression of time spent in the food zone. The multiple treatments over 4 days gave the same results.

Scopinho et al. (2011) treated Wistar rats that had free access to food or animals that had been fasted for 18 hours with a single i.p. injection of 1, 10, or 20 mg/kg CBD. After 30 minutes, the rats were provided food. While CBD alone had no effect on food intake, CBD was able to prevent the hyperphagia seen in rats that had also been treated with agonists to CB1 or 5-HT$_{1A}$ receptors.

Farrimond et al. (2012) treated rats with CBD (doses 0.04 mg/kg, 0.44 mg/kg, 4.4 mg/kg) and tested later for food intake. Only doses of 4.4 mg/kg demonstrated a statistically significant decrease in cumulative food intake when measured over 1-4 hours after treatment.

1.2.2.2. Multiple Dose Regimens

Ignatowska-Jankowska et al. (2011) treated male Wistar rats at an age when body weight is rapidly increasing with i.p. injections at doses of 2.5 mg and 5 mg/kg/day for 14 consecutive days. The diet provided was standard *ad lib* rodent chow without prior fasting. Both CBD doses produced significant decreases in body weight gain, with the effect produced by the 5 mg/kg dose being more pronounced. This effect on weight was blocked, however, by a selective CB2 antagonist, raising the possibility of more peripheral, non-CNS mechanism.

Wierucka-Rybak et al. (2014) reported a study where CBD alone or in combination with leptin were administered intraperitoneally to Wistar rats for 3 consecutive days and maintained on either a high-fat diet or free choice diet consisting of high-sucrose and normal rat chow. Interestingly, while CBD seemed to decrease food intake on rats feed high fat diet or standard chow, there did not seem to be corresponding decrease in weight after the 4 days of the study.

Rhesus monkeys treated with oral CBD for 90 consecutive days (30-300 mg/kg/day; 4 monkeys/sex/dose) to observe toxicities demonstrated a relative dose-dependent decrease in weight gain. As it was reported as an observation, it did not merit comment by the authors (Rosenkrantz et al., 1981).

While animal models provide seemingly inconsistent results on the effect of CBD on food intake and weight, they nonetheless suggest a potential non-acute effect on appetite and overall food consumption. This likely indicates, more than anything, the complex interaction between the endocanniboid system with appetite regulation (via the leptin and ghrelin), the endogenous reward system mediated by the cholinergic-serotinergic pathway, and metabolic regulation. The observation that some studies have demonstrated that CBD up to 80-100 mg/kg had no acute (within 24 hours) effect on food consumption in mice and rats, but did so in longer test periods provides support for the length of the current study of 12 weeks.

1.3. Clinical Experience

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

- Cannabidiol levels on Day 10 appeared to increase proportionally with weight-based dose across the dosing cohorts, notwithstanding the two different formulations of the investigational product.
- Steady-state levels of cannabidiol appeared to be attained with approximately 2 to 6 days of repeated BID dosing with Cannabidiol Oral Solution, with geometric mean area under the concentration-time curve in plasma during a dosing interval ($AUC_{(0\text{-}tau)}$) of 507.0 (Cohort 1 [10 mg/kg/day]), 836.0 (Cohort 2 [20 mg/kg/day]), and 2108 ng·h/mL (Cohort 3 [40 mg/kg/day]) for all age categories combined.

- Geometric mean maximum plasma concentrations (C_{max}) of cannabidiol at steady-state were 91.0 (Cohort 1 [10 mg/kg/day]), 126.0 (Cohort 2 [20 mg/kg/day]), and 314.5 ng/mL (Cohort 3 [40 mg/kg/day]) for all age categories combined.
- Median time to maximum plasma concentration of cannabidiol at steady-state ranged from 2.0 to 3.0 hours for all age categories combined.
- Geometric means of cannabidiol apparent terminal half-life ($t_{1/2}$) ranged from 19.5 to 29.6 hours following a single dose of Cannabidiol Oral Solution for all age categories combined.
- Accumulation in cannabidiol exposures was approximately 3- to 4-fold for all age categories combined. Dosing cohort total geometric means ranged from 2.6 to 3.1 for accumulation ratio for C_{max} and from 3.6 to 4.4 for accumulation ratio for $AUC_{(0\text{-}tau)}$.
- Most of the dosing cohort's total variability in cannabidiol exposures after repeated dosing (Day 10) was lower than Day 1. Single and repeated administrations of Cannabidiol Oral Solution resulted in highly variable systemic exposures of cannabidiol.
- There were no apparent formulation-related differences observed in terms of $t_{1/2}$, dose-normalized exposures, and variability.
- There were no clear trends for age-related differences in cannabidiol exposures, but exposure in infants tended to be lower than that in children and adolescents, approximately half at the highest dose (40 mg/kg/day).
- Approximately 50% of subjects enrolled were receiving clobazam. Clobazam and cannabidiol have a reciprocal drug-drug interaction leading to the increased mean exposures of both cannabidiol (approximately 2.5-fold), and clobazam as well as norclobazam (approximately 3-fold) at the highest dose (40 mg/kg/day).
- No apparent gender differences were observed for cannabidiol pharmacokinetics (PK).
- Pharmacokinetic results for 7-hydroxy cannabidiol and its statistical evaluations generally reflected those observed for parent cannabidiol.
- There were no quantifiable levels Δ^9-THC and 11-hydroxy-Δ^9-THC measured following cannabidiol dosing.
- All doses of the investigational product were generally well-tolerated, although dose-titration was not employed. Dose-dependent adverse events (AEs) that occurred in multiple dosing cohorts and increased as the dose of the investigational product increased included diarrhea, flatulence, weight increase, somnolence, and psychomotor hyperactivity. Events of somnolence were potentially also related to concomitant use of clobazam with the investigational product, but this was not formally investigated in this study.
- There were no clinically relevant differences in the AE profile among subjects in the infant, child, and adolescent age categories.
- Serious adverse events were reported rarely and were consistent with underlying disease or procedures.

- Although this was not designed as an efficacy study, parent(s)/caregiver(s) and investigators both reported notable reductions in severity of mental illness (Clinical Global Impression of Severity) and improvement in global subject status (Clinical Global Impression of Improvement).
- The average change in weekly seizure rates (seizures of all types) was variable across subjects, dosing cohorts, and over time. Although the mean change in the weekly rate of tonic seizures at the end of the study compared with baseline generally decreased in a potentially dose-dependent manner, no pattern was observed for the other types of seizures reported. It was thought that tonic seizures were most representative of seizure control in this study.

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

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

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

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

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

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

Overall, over 100 patients have been treated with Cannabidiol Oral Solution, many for over 48 weeks, ranging in age from 1-51 years and was generally well-tolerated. A summary of the clinical experience is summarized below in Table 2.

A Phase 1/2 study to assess the pharmacokinetics and safety of multiple doses (10 mg/kg/day, 20 mg/kg/day, and 40 mg/kg/day) of pharmaceutical Cannabidiol Oral Solution in pediatric subjects with treatment-resistant seizure disorders was conducted by the Sponsor (Protocol INS011-14-029). This study has been completed and the data were presented. In addition, a long-term safety study (Protocol INS011-14-030) for subjects who enrolled in the PK study above recently completed.

An open-label study of Cannabidiol Oral Solution (20 mg/kg/day and 40 mg/kg/day) in pediatric subjects with infantile spasms refractory to adrenocorticotropic hormone (ACTH) and vigabatrin was also conducted and discussed below (Protocol INS011-14-054).

Two food effect studies of Cannabidiol Oral Solution in normal healthy adults (Protocol INS011-14-043) and (Protocol INS011-16-093) were also conducted.

Table 2: List of Insys Sponsored Clinical Trials with Cannabidiol Oral Solution

Study Number	Study Title	Study Design	Population	Number of Patients	Study Status
INS011-14-029	A Phase 1/2 study to assess the pharmacokinetics and safety of multiple doses of pharmaceutical Cannabidiol Oral Solution in pediatric subjects with treatment-resistant seizure disorder.	Open label	Pediatric patients (1 to 17 years of age) with refractory epilepsy	61	Completed
INS011-14-030	A multicenter, open-label, flexible dose study to assess the long-term safety of pharmaceutical Cannabidiol Oral Solution as an adjunctive treatment for pediatric and adult subjects with a treatment-resistant seizure disorder who complete INS011-14-029, INS011-024, or INS011-14-025.	Open label	Pediatric patients (1 to 17 years of age) with refractory epilepsy	52	Completed
INS011-15-043	An open-label, randomized, single-dose, two-period, two-way crossover food-effect study of Cannabidiol Oral Solution in healthy subjects.	Open label	Healthy adults	24	Completed

Study Number	Study Title	Study Design	Population	Number of Patients	Study Status
INS011-15-054	A Phase 2 study to assess the efficacy and safety of Cannabidiol Oral Solution for the treatment of refractory infantile spasms	Open label	Infants 6 to 36 months with infantile spasms refractory to ACTH and vigabatrin	9	Completed
INS011-16-093	A Phase 1, open-label, randomized, single-dose, four-treatment, four-sequence, four-period, four-way crossover food effect study of multiple formulations of Cannabidiol Oral Solution in healthy subjects.	Open label	Healthy adults	8	Completed

1.3.1. Pharmacokinetics

INS011-14-029 is a completed Phase 1/2 study assessing the pharmacokinetics (PK) and safety of multiple doses of pharmaceutical CBD (Cannabidiol Oral Solution, Insys Development Company, Inc.). Each cohort of 20 pediatric patients from 1 to 17 years of age was administered 10 mg/kg/day, 20 mg/kg/day, or 40 mg/kg/day over a period of 10 days. Patients were dosed as inpatients for Days 1 through 8. Patients were then offered the opportunity to be discharged on Day 8 with readmission on Day 10 for a final study assessment on Day 11. Cohort 1 received an earlier formulation containing alcohol; Cohorts 2 and 3 received a subsequent alcohol-free, medium chain triglyceride (MCT)-containing formulation. The study was designed to have adequate representation among three age groups in each dosing cohort: infants (1 to <2 yrs: 5 subjects), children (2 to <12 yrs: 9 subjects), and adolescents (12 to <18 yrs: 6 subjects).

Single oral administration of CBD at 5, 10, 20 mg/kg (half of the full daily dose) resulted in mean peak levels of about 59, 111, and 232 ng/mL, respectively. The PK of CBD in different age groups was comparable at each dose level. Steady-state seemed to be achieved within 2 to 4 days after twice daily doses of 5, 10, 20 mg/kg/day CBD, with typical steady-state peak levels of about 120, 214, and 427 ng/mL, respectively.

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

The food effect study (Protocol INS011-15-043) demonstrated that when taken within 30 minutes of the start of a meal, CBD mean AUC and C_{max} were significantly higher with a much improved (lower) coefficient of variance and a 6-hour shorter median time to maximum concentration (T_{max}). Thus, there is a recommendation that all doses be administered within 30 minutes after the start of a meal.

Insys Study INS011-16-093 examined three different formulations under fed with standard high-fat diet and/or fasted conditions: sesame-oil based, 100 mg/mL (fed and fasted), MCT-based, 100 mg/mL (fed) and alcohol-containing, 80 mg/mL). An appreciable food effect and lower variability were observed with

the Cannabidiol Oral Solution (100 mg/mL) in a Sesame Oil Formulation, with mean exposures of 6.9-fold and 11.9-fold higher, for AUC_{0-t} and C_{max}, respectively, relative to the fasted state. All formulations (Sesame Oil, Medium Chain Triglyceride, and alcohol-containing) showed similar exposures in the fed state. Mean (standard deviation [SD]) AUC_{0-inf} (h*ng/mL) in the fed condition was: 4450 (1130) for Sesame Oil based, 4360 (933) for MCT-based, and 4980 (2110) for alcohol-containing. The %CV was 25.3, 21.4, and 42.3 for Sesame-Oil based, MCT-based, and alcohol-containing, respectively.

As a comparison, mean peak and total exposures in all age groups (Protocol INS011-14-029) on Day 10 were within 16 to 36% to dose-adjusted exposures in fed adults (Protocol INS011-15-043). Thus, similar PK parameters are expected to operate over this study's age range of 8-17 years of age.

1.3.2. Overview of Safety

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

Clinical studies in various human populations indicate that CBD has a favorable side-effect profile. Doses as high as 1500 mg were well tolerated (Zuardi et al., 1995). 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. (2011b) recently reviewed the safety of CBD in humans examined in 221 subjects across 21 studies. As detailed in the IB, no significant safety issues were reported.

Regarding doses of CBD that have been examined in other studies, daily doses of 200 to 300 mg CBD (or potentially more) may be safe (Cunha et al., 1980; Gloss and Vickery, 2014). Clinical evaluation and therapeutic ranges of CBD doses have been reported to be between 10 and 1500 mg/day, with the majority of reports evaluating doses in the 300 to 600 mg/day CBD range. Furthermore, between 300 and 1500 mg have been used in humans without toxicity or SAEs (Consroe et al., 1991; Zuardi et al., 1993, 1995; Borgwardt et al., 2008).

In Study INS011-14-029 and the subsequent extension study, INS011-14-030, some patients received over 3000 mg/day for several months without toxicity or SAE.

1.3.3. Clinical Safety Data

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

- Daily dosing of 10 mg/kg CBD was evaluated in a study of 15 subjects diagnosed with Huntington's disease (Consroe et al., 1991). Only 15 abnormal clinical laboratory values were associated with CBD treatment; these were largely limited to 4 subjects and exhibited no obvious pattern. No significant or clinical differences in CBD were observed in a cannabis-specific side-effect inventory.
- Chronic oral administration of 10 mg CBD daily for 21 days does not induce any changes in neurological (including electroencephalogram [EEG]), clinical (including electrocardiogram [ECG]), psychiatric, blood, or urine examinations in both healthy volunteers and epileptic subjects (Cunha et al., 1980).
- Oral administration of CBD in healthy volunteers (3 mg/kg daily for 30 days) and in epileptic subjects (200 to 300 mg daily for 135 days) was well tolerated. No signs of

toxicity or serious side-effects were detected on neurological and physical examinations, blood and urine analysis, ECG, or EEG (Cunha et al., 1980; Gloss and Vickery, 2014).

- Administration of single and repeated doses of CBD for up to 20 days at a dose of 1200 mg/day does not impact pulse rate and blood pressure in human subjects with previous experience to cannabis smoking (Gong et al., 1984).
- Three subjects with treatment-resistant schizophrenia have been dosed with 40 to 1280 mg/day of CBD for up to 4 weeks without reporting side-effects (Zuardi et al., 2006).
- Two subjects diagnosed with bipolar affective disorder did not report adverse effects upon receiving 600 to 1200 mg/day of CBD for up to 24 days (Zuardi et al., 2010).
- Insys recently completed a long-term safety study (INS-011-030, 48 weeks) for pediatric subjects who were receiving up to 40 mg/kg/day (maximum dose given was 3200 mg/day) in the Phase 1/2 PK study (Protocol INS011-14-029) and these doses were generally well tolerated.
- There is currently an expanded access program ongoing for the pediatric patients who completed the long-term safety study (INS-011-030) and wished to continue on CBD therapy.

In addition to the references cited above, there are recently published studies of CBD treatment of refractory epilepsy.

In an open label study of Epidiolex® (a plant-derived purified CBD), 214 patients suffering from different refractory epilepsies were enrolled between January 15, 2014, and January 15, 2015 (Devinsky et al., 2016). Patients were given oral cannabidiol at 2-5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site), for a 12-week treatment period. Titration to a maximum dose of 50 mg/kg per day was done in 48 (30%) patients, 23 of whom received a dose of more than 25 mg/kg per day during the 12-week treatment period. Of the 214 enrolled patients, 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis, 137 (64%) patients were included in the efficacy analysis.

The most common adverse events reported (in more than 10% of patients) were somnolence (n=41, 25%), decreased appetite (n=31, 19%), diarrhea (n=31, 19%), fatigue (n=21, 13%), and convulsion (n=18, 11%). Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, including one death-a sudden unexpected death in epilepsy regarded as unrelated to study drug; 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]).

In a Phase 3 study, 171 patients aged 2 to 55 years with a confirmed diagnosis of drug-resistant Lennox–Gastaut Syndrome (LGS) currently uncontrolled on one or more concomitant AEDs were randomized into two treatment arms, Epidiolex® 20 mg/kg/day (n=86) or placebo (n=85), for a 14-week treatment period (Thiele et al., 2016). Epidiolex® or placebo was added to current AED treatment regimens. On average, patients were taking approximately 3 AEDs, having previously tried and failed an average of 6 other AEDs. The average age of patients was 15 years. Epidiolex® was generally well tolerated in this trial. Overall, 86% of all Epidiolex®

patients experienced an adverse event compared with 69% of patients on placebo. The most common adverse events (occurring in greater than 10% of Epidiolex®-treated patients) were: diarrhea, somnolence, decreased appetite, pyrexia, and vomiting. Twenty patients on Epidiolex® experienced a serious adverse event (nine of which were deemed treatment related) compared with four patients on placebo (one of which was deemed treatment related). Twelve patients on Epidiolex® discontinued treatment due to adverse events compared with one patient on placebo. There was one death in the Epidiolex® group, which was considered unrelated to treatment.

In another Phase 3 study, 120 patients aged 2 to 18 years with Dravet Syndrome were randomized into two treatment arms, Epidiolex® 20 mg/kg/day (n=61) and placebo (n=59), for a 14-week treatment period (Devinsky et al., 2017). Epidiolex® or placebo was added to current AED treatment regimens. On average, patients were taking approximately three AEDs, having previously tried and failed an average of more than four other AEDs. The average age of trial participants was 10 years and 30 percent of patients were less than 6 years of age. Epidiolex® was generally well tolerated in this study. The most common adverse events (AEs) (occurring in greater than ten percent of Epidiolex®-treated patients) were: somnolence, diarrhea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection, and convulsion. Ten patients receiving Epidiolex® experienced a serious AE compared with three patients receiving placebo. None of these events led to withdrawal from the study and none were considered related to the study treatment.

In Study INS011-14-029, the most common adverse events included somnolence (21.3%), diarrhea (16.4%), anemia (18%), psychomotor hyperactivity (8.2%), and flatulence (8.2%). Somnolence may have been related to the concomitant administration with the anti-epileptic, clobazam, that resulted in increased plasma levels of clobazam due to a unique drug-drug interaction. The somnolence improved following dose adjustments. Somnolence was observed in only 3.3% of study subjects who were not taking clobazam. In addition, three serious adverse events were observed following administration of drug (three were observed after screening but before dosing). The first involved the development of a thrombus associated with a peripherally inserted central catheter (PICC) line in an infant. The thrombus resolved with treatment without any untoward effects. The second involved an apneic episode felt to be related to gastroesophageal reflux disease (GIRD) also in an infant. Neither of these SAEs were deemed by the investigator to be related to the drug. The third SAE consisted of a drug eruption following the final dose of the study that self-resolved without intervention.

In the long-term safety study, INS014-030, 52 patients continued treatment for approximately 48 weeks at doses ranging from 10 mg/kg/day to 40 mg/kg/day. Cannabidiol Oral Solution was generally safe and well-tolerated. The most frequently reported AEs were seizure, upper respiratory tract infection, anemia, diarrhea, pyrexia, somnolence, aggression, nasopharyngitis, and otitis media; anemia and somnolence were considered related to study drug. Seventeen subjects experienced serious TEAEs; the most frequently reported serious TEAEs were seizure, status epilepticus, and mental status changes (all considered unrelated to study drug). These events may have been consistent with the subjects' underlying disease and seizure history. One subject died during the study due to systemic sepsis that was considered unrelated to investigational product. Dose reductions occurred for 26.9% of the patients; primarily at the 40 mg/kg/day dose (9/20 patients, 45.0%).

In summary, the safety data to date suggest that cannabidiol can be safely administered to and tolerated by medically complex pediatric and adult patients at doses up to 40 mg/kg/day for extended periods of time (currently over 48 weeks). Despite the confounding co-administration of clobazam in the majority of cases of observed somnolence, CBD should be carefully monitored in patients with significant respiratory comorbidities, such as those that occur in patients with Prader-Willi Syndrome.

1.4. Prader-Willi Syndrome

Prader-Willi Syndrome (PWS), first described in 1956, is a multifaceted developmental disorder and the most common genetic syndrome associated with obesity (Gunay-Aygun et al., 1997; McAllister and Whittington, 2011). It is caused by the absent expression of paternally-inherited genes in the PWS region on 15q11-q13 (Ledbetter et al., 1981). While it presents with generalized hypotonia and developmental delay in infancy, PWS then manifests with uncontrollable appetite, hyperphagia, and excessive weight gain leading to severe obesity (Grechi et al., 2012).

Clinically, PWS patients suffer a complex pattern of physical, behavioral, endocrine, and intellectual deficiencies. Endocrine abnormalities lead to hypogonadism and short stature. In particular, growth hormone deficiency is reported to occur in 40% to 100% of the population (Griggs et al., 2015) and is commonly treated with growth hormone (Angulo et al., 2015). Behavioral disorders include obsessive compulsive behaviors such as skin picking, hoarding, re-doing, and repetitive speech (Griggs et al., 2015).

However, it is the appetite behavior classified as hyperphagia in Prader-Willi Syndrome that is the most life threatening (Dykens et al., 2007; Griggs et al., 2015) and until recently, no patient lived over the age of 50 due to morbid obesity and its related complications (Aycan et al., 2014). The mortality rate in patients with PWS is six times higher than patients with other intellectual disabilities (Einfeld and Kavanagh, 2006) and mortality in patients not treated with growth hormone was estimated to be 3% per year between the ages of 6 and 56 compared to the general population mortality of 0.13% below 55 years. Mortality in Prader-Willi Syndrome below 5 years of age has not been determined (Eiholzer, 2005).

Hyperphagic behaviors can also be dangerous in persons who are not obese, with increased risks of death due to choking while sneaking food, and gastric perforations after consuming more food than usual (Dykens et al., 2007). Approximately 8% of deaths in individuals with PWS are reported due to the choking, especially on hot dogs (Stevenson et al., 2007). PWS patients also are known to eat discarded (contaminated) food and items that are not for human consumption such as pet food, or even non-food items such as paint or paper (Griggs et al., 2015).

Currently, there are no FDA-approved therapies for the treatment of hyperphagia or obesity in patients with PWS. In addition, drugs that have demonstrated efficacy in the past have been withdrawn or have significant safety concerns (e.g., rimonabant, beloranib). Therapy consists mostly of strict and consistent behavioral controls surrounding eating that prevent independent living for adult patients. Recent studies investigating modulation of the endocannabinoid system, however, have shown promise.

The endocannabinoid system appears to be critically involved in the regulation of appetite, body weight, metabolism, hypothalamic-pituitary-adrenal axis, and reward brain circuitry (Liu et al.,

2005; Edwards and Abizaid, 2016). Endocannabinoid receptor CB1, is widely expressed in the central nervous system, autonomic gastric vagus nerve endings of the peripheral nervous system, and other key cells involved in body energy metabolism, including adipocytes, hepatocytes, and myocytes (Bensaid et al., 2003; Liu et al., 2005; Osei-Hyiaman et al., 2008). In clinical studies, compounds with endocannabinoid effects (fenfluramine, rimonabant) have shown significant effects on weight and appetite suppression (Pinder et al., 1975; Despres et al., 2005; Pi-Sunyer et al., 2006). These effects on appetite also occurred in 19% of epilepsy patients treated with Epidiolex® (i.e., cannabidiol extracted from the cannabis plant) during an open-access program for patients with pediatric seizure disorder (Devinsky et al., 2016). Because of the well-characterized orexigenic activity of THC (a strong CB1 agonist), the CB1 antagonist, rimonabant, was studied and found to be effective in treating obesity in adults without PWS (Pi-Sunyer et al., 2006). Both fenfluramine and rimonabant were subsequently withdrawn from the market, however, due to unacceptable side effects (McCann et al., 1997).

CBD is a low-affinity antagonist of CB1, but it may also modulate CB1 receptor signaling through its inhibition of the metabolism of the endogenous cannabinoid, anandamide (Ibeas Bih et al., 2015; Laprairie et al., 2015). As for appetite, CBD has been shown to decrease food intake in rats under stressful conditions and reduce *ad lib* intake of high-sugar feed when compared to vehicle-treated controls (Silveira Filho and Tufik, 1981). In addition, CBD has been shown to diminish daily food consumption without affecting daily water intake (Wierucka-Rybak et al., 2014) as well as inhibited hyperphagia induced by CB1 receptor or 5-hydroxytryptamine (5-HT_{1A}) serotonin receptor agonists suggesting a role for CBD as a regulator of food intake. Perhaps just as importantly, CBD decreases cue-induced craving and reduces the reward induced by drugs of abuse by modulating the cholanergic-dopaminergic pathway that may drive such behaviors in PWS patients (Von Deneen et al., 2009; Hurd et al., 2015; Parsons and Hurd, 2015).

Thus, CBD may have potential to address the main medical problems associated with Prader-Willi Syndrome patients leading to obesity and related mortality. Insys Development Company, Inc. (Insys) is manufacturing a pharmaceutical grade synthetic cannabidiol formulation (Cannabidiol Oral Solution) to be advanced into clinical development for the treatment of hyperphagia behaviors and obesity in patients with Prader-Willi Syndrome.

1.5. Dose Selection Rationale

Patients total daily dose will range from 20 mg/kg/day, 30 mg/kg/day, and 40 mg/kg/day. Doses of CBD may be adjusted at the investigator's discretion up to a maximum of 40 mg/kg/day. Doses greater than 40 mg/kg/day are not allowed.

1.6. Summary of Potential Risks and Benefits

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

- Competitive binding of CYP proteins (thus, an impact on drug metabolism in the liver). Cannabidiol is metabolized predominantly by CYP3A4 and CYP 2C19. Cannabidiol may inhibit these two isozymes, as well as having small effects on CYP3A5, CYP2D6, CYP1A1, and CYP2C9.

- Potential downregulation of immune responses involving the T, B, T-helper, and T cytotoxic subsets of leukocytes and/or those dependent on IL-2 or IFN-γ.

Based on recent studies of cannabinoid administration in humans, controlled CBD may be safe in humans and animals. While further studies are needed to clarify these reported *in vitro* and *in vivo* side-effects (Braut-Boucher et al., 1986), no infection-related events have been reported in recent studies in the pediatric seizure population.

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

Criteria for removal of subjects from the study and stopping rules will dictate discontinuation of subject participation should a safety issue arise (see Section 3.3 and Section 3.5, respectively).

The appetite behavior classified as hyperphagia in Prader-Willi Syndrome is the most life threatening (Dykens et al., 2007; Griggs et al., 2015) and until recently, no patient lived over the age of 50 years due to morbid obesity and the related complications (Aycan et al., 2014). The mortality rate in patients with PWS is six times higher than patients with other intellectual disabilities (Einfeld and Kavanagh, 2006) and mortality in patients not treated with growth hormone was estimated to be 3% per year between the ages of 6 and 56 years compared to the general population mortality of 0.13% below 55 years; mortality in Prader-Willi Syndrome below 5 years of age has not been determined (Eiholzer, 2005).

Hyperphagic behaviors can also be dangerous in persons who are not obese, with increased risks of death due to choking while sneaking food, and gastric perforations after consuming more food than usual (Dykens et al., 2007). Approximately 8% of deaths in individuals with PWS was reported due to the choking, especially on hot dogs (Stevenson et al., 2007). Prader-Willi Syndrome patients also are known to eat discarded (contaminated) food and items that are not for human consumption such as pet food, or even non-food items such as paint or paper (Griggs et al., 2015).

Subjects with PWS continue to experience a significant unmet medical need, especially when it comes to hyperphagia behavior and obesity. There are no approved drugs currently to treat these behaviors. Fenfluramine demonstrated significant efficacy in Prader-Willi Syndrome patients but was removed from the market due to cardiac valve concerns. Rimonabant was approved in the EU for obesity and a trial was ongoing in Prader-Willi Syndrome. However, the drug was never approved in the US and removed from the market in the EU due to significant psychiatric side effects. A trial in PWS, while demonstrating a trend for efficacy was terminated early for safety concerns. Currently, Zafgen's product Beloranib demonstrated significant positive effects on weight loss and hyperphagia behavior in patients with Prader-Willi syndrome but is currently on hold due to two deaths that were thought to be caused by thrombotic events. Orlistant, locaserin, Qsymia, and Contrave have been approved for obesity but not studied in the Prader-Willi Syndrome population. Therefore, there continues to be a high unmet need for an efficacious and safe treatment for this population.

Cannabidiol has been safely administered to over 300 medically complex children and was generally well-tolerated. The adverse events recorded do not correspond to those encountered by previous trials in patients with Prader-Willi syndrome. The anxiolytic effects of CBD and its indirect effect on the CB1 receptor suggest an improved side effect profile in this population.

In conclusion, there is both pre-clinical and clinical evidence that affecting the endocannabinoid system with cannabidiols, including cannabidiol, may demonstrate a clinically relevant effect on the hyperphagia behaviors as well as lead to weight loss in patients with Prader-Willi Syndrome. Insys believes that due to the safety and tolerability of cannabidiol demonstrated by the data available in the literature and collected by the sponsor, and the life-threatening obesity in Prader-Willi Syndrome, the demonstration of efficacy and safety of Cannabidiol Oral Solution in this population will be a valuable option to treat these patients.

2. STUDY OBJECTIVE

The objective of this study is to assess the long-term safety and tolerability of Cannabidiol Oral Solution (CBD) in patients with Prader-Willi Syndrome.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a multicenter, open-label study designed to assess long-term safety and tolerability of CBD in patients with Prader-Willi Syndrome. Patients must have completed INS011-16-085 to be eligible.

The investigator will ensure that the patients legal representative [parent(s)/caregiver(s)] will receive a copy of the informed consent form for review and provide full informed consent prior to study participation. Patients may enroll in this long-term safety study (INS011-17-115) after completing INS011-16-085 Visit 10 (Study Completion) to avoid interruption of the investigational product. Patients will have up to 2 weeks to enroll in INS011-17-115.

Patients will receive CBD treatment for approximately 48 weeks. Total daily doses ranging from 20 mg/kg/day to 40 mg/kg/day will be administered with standard meal. If any participant does not enroll within the 2 week window, that patient will not be eligible to enroll into the study.

The study will consist of a Safety Period (48±2 weeks), Taper Period (6±3 days), and a Follow-up Period (30±5 days). Treatment visits will be scheduled monthly for the first 3 months and then quarterly over the remaining 9 months. All patients will complete a Visit 7 (End of Study) or Early Withdrawal Visit regardless of when they stop treatment/complete the study. A Follow-Up telephone call (Visit 9) will occur 30 days after the end of either the End of Study (Visit 7) or Early Withdrawal.

Once the informed consent for INS011-17-115 is provided within the required time frame, the patient will receive a total daily dose ranging from 20mg/kg/day to 40mg/kg/day.

Patients will be dosed approximately every 12 hours with food to help ensure consistent plasma levels are achieved. Patients will be dosed for 48 weeks during which the investigator will assess safety and tolerability.

The study will be terminated upon one of the following:

- The investigational product is successfully approved for marketing in the US.
- Sponsor elects to terminate INS011-17-115.
- The patient has received 48 weeks of treatment.

3.1.1. Safety Assessments

At Visit 1 (Day 1) and each monthly and quarterly visit, the following assessments will be completed:

- Review vital signs, clinical labs, ECG, urinalysis (Visit 1 only), urine preganacy screen, urine drug screen, weight and physical examination.
- Review concomitant medication and adverse events (AEs).
- 12-lead ECG.

- Columbia-Suicide Severity Rating Scale (C-SSRS) will be used for children and adolesents aged 7 to 17 years, if appropriate.
- Dispensing CBD.
- Drug accountability.

At Visit 7 (End of Study) or Early Withdrawal Visits the following assessments will be completed:

- Review vital signs, clinical labs, ECG, urinalysis, urine preganacy screen, urine drug screen, weight and physical examination.
- Review concomitant medication and adverse events (AEs).
- 12-lead ECG.
- Columbia-Suicide Severity Rating Scale (C-SSRS) will be used for children and adolesents aged 7 to 17 years, if appropriate.
- Hyperphagia Questionnaire for Clinical Trial (HQ-CT).
- Dispensing CBD.
- Drug accountability.

All AEs that arise during the Safety, Taper, and Follow-up Periods will be documented.

3.1.2. Taper Period

At the end of the Long-Term Safety study patients will be tapered off of CBD over a 0-6 day period. The following tapering scheme will be utilizied: 40 mg/kg/day will be reduced to 30 mg/kg/day for three days, then 30 mg/kg/day will be reduced to 20 mg/kg/day for three days and then discontinued; 30 mg/kg/day will be reduced to 20 mg/kg/day for three days and then discontinued. This can be modified by the investigator based upon the patient's response

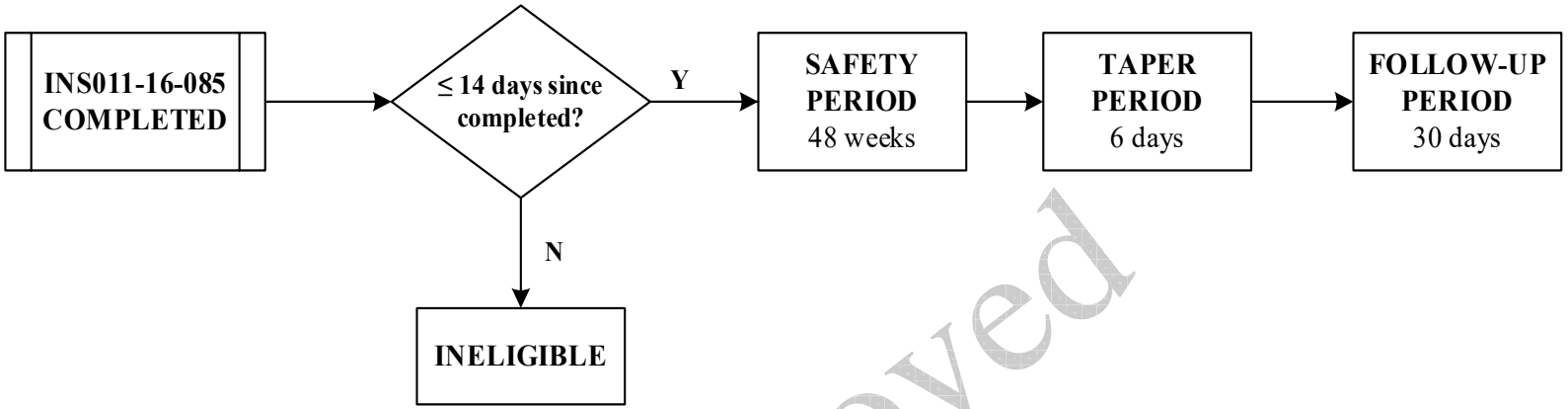
Tapering will occur under the following circumstances:

- Patient completes Visit 7 (End of Study). Patient will begin tapering the day after Visit 7.
- Patient withdraws early. Patient will begin tapering the day after the investigatory has been informed of the decision to withdraw from the trial.

3.1.3. Follow-Up Period

A follow-up telephone call (Visit 9) will occur 30 days after the Visit 7 (End of Study) or Early Withdrawal to assess AEs and record concomitant medications.

Figure 1: Study Design Schematic



3.2. Patient Selection

3.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria:

1. Completed all activities through Visit 10 (Study Completion) of INS011-16-085.
2. Patient and/or parent(s)/caregiver(s) fully comprehend the informed consent form (ICF) and assent form, understand all study procedures, and can communicate satisfactorily with the investigator and study coordinator, in accordance with applicable laws, regulations, and local requirements.
3. If female, is either not of childbearing potential (defined as premenarchal or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing one of the following medically acceptable methods of birth control:
   a. Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives for a minimum of 1 full cycle (based on the patient's usual menstrual cycle period) before study drug administration.
   b. Total abstinence from sexual intercourse since the last menses before study drug administration.
   c. Intrauterine device.
   d. Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream).
4. Psychotropic treatment will be permitted if the subject has been on a stable dose during the INS011-16-085 and does not anticipate a dose change during the course of the study.
5. Growth hormone treatment will be permitted if the subject has been on a stable dose during INS01-16-085.
6. Any other treatment including thyroid hormones should be stable prior to entering the INS011-17-115 study.
7. In the opinion of the investigator, the parent(s)/caregiver(s) is (are) willing and able to comply with the study procedures and visit schedules, including venipuncture, and the visit schedules.

3.2.2. Exclusion Criteria

Patients will be excluded for any of the following:

1. Patient or parent(s)/caregiver(s) have daily commitments during the study duration that would interfere with attending all study visits.
2. Experienced an anoxic episode related to study drug requiring resuscitation during their previous study.
3. Uncontrolled Type I and Type II diabetes.

4. Developed an adverse event thought to be related to CBD in the previous study and for whom the Investigator determines that continuing treatment with CBD would not be in the best interest of the patient.
5. History of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or other condition which would jeopardize safety or impact validity of results (per investigator).
6. Currently taking felbamate.
7. Compromised respiratory function or severe respiratory insufficiency.
8. Pregnant or lactating female.
9. In the opinion of the investigator, the patient is unsuitable in any other way to participate in this study.

3.3. Removal of Patients from Therapy or Assessment

Patients will be allowed to discontinue their participation in the study at any time for any reason (withdrawal of consent). Furthermore, participation in this clinical study may be discontinued by the Investigator or by the sponsor for any of the following reasons:

- Intolerable side effects of the study product.
- Changes in medical status or medical condition of the patient such that the Investigator believes that patient safety will be compromised or that it would be in the best interest of the patient to stop treatment.
- Pregnancy.
- Relevant non-compliance with the protocol.
- Any use of marijuana, confirmed by a positive drug screen for THC.

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

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

3.4. Dose Adjustment Criteria

Patients may have their dose of study medication adjusted down once from 40 mg/kg/day to 30 mg/kg/day or 30 mg/kg/day to 20 mg/kg/day at the discretion of the Investigator or qualified designee based on the patient's tolerability. If the lower dose is not tolerated, the drug will be discontinued and the patient will be withdrawn from the study.

All dose changes must be clearly documented in the eCRF.

3.5. Stopping Rules

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

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

4. TREATMENTS

4.1. Treatments Administered

Patients or parent/caregiver will be reminded how to measure, take their dose, and record their dose in the dosing diary when the IP is dispensed for the first time.

Total daily doses between 20 mg/kg/day, 30 mg/kg/day, and 40 mg/kg/day will be administered with standard meal, in two equivalent daily doses approximately every 12 hours.

4.2. Identity of Investigational Product

The active pharmaceutical ingredient (API) in Cannabidiol Oral Solution is a pharmaceutical grade synthetic CBD manufactured according to cGMP. It is an off-white to pale yellow resin or crystal substance that is soluble in several organic solvents with an acid dissociation constant (pKa) of 9.64. The solution is a clear, colorless to pale yellow-brown colored solution (CBD concentration of 100 mg/mL) filled into a 30 mL amber glass vial. More detailed information may be found in the IB.

4.3. Selection of Doses in the Study

Patients total daily dose will ranging from 20 mg/kg/day, 30 mg/kg/day, and 40 mg/kg/day. Doses of CBD may be adjusted at the investigator's discretion up to a maximum of 40 mg/kg/day. Doses greater than 40 mg/kg/day are not allowed

4.4. Selection and Timing of Dose for Each Patient

Once the informed consent for INS011-17-115 is provided, patients will initiate this long-term safety study. Total daily dose will range from 20 mg/kg/day, 30 mg/kg/day, and 40 mg/kg/day.

Patients will take each dose approximately every 12 hours with standard meal in order to ensure consistent plasma levels are achieved. The date and time of all investigational product administrations will be documented in the case report form (CRF).

4.5. Blinding and Unblinding Treatment Assignment

Not applicable. This is an open-label study.

4.6. Treatment Compliance

The prescribed dosage, timing, and mode of administration of IP may not be changed except as directed by the investigator.

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

All supplies of IP should be accounted for at the termination of the study and a written explanation provided for discrepancies. All used and unused supplies, and packaging materials are to be inventoried and returned to the Sponsor or a designee by the investigator. The

investigator is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by the Sponsor or a designee.

If the study is terminated, discontinued, suspended, or completed, all used and unused supplies of the investigational product may be destroyed via the use of a third-party vendor or be returned to the Sponsor or a designee after the final drug accountability check has been performed. A certificate of destruction will be provided to the Sponsor.

All regulations issued by the DEA concerning the accountability of Schedule I medications will be followed (e.g., prevention of diversion).

4.7. Permitted and Prohibited Therapies

4.7.1. Permitted Therapies

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

Growth hormone, thyroid hormone, and psychotropic medications are permitted, provided they meet the stability requirements described in the inclusion criteria.

Adjustments to growth hormone and thyroid hormone medications are permitted as needed based on weight. Laboratory assessments for IGF-1/BP3 are required one month after any changes to growth hormone medication, and assessments for FT4 and TSH are required one month after any changes to thyroid hormone medication. No changes to psychotropic medications are allowed.

4.7.2. Prohibited Therapies

During the Safety, Taper, and Follow-up Periods, patients are not to receive the following:

- Any cannabinoids other than study medication (CBD, Δ^9-THC, hemp oil, Realm Oil or marijuana).
- Felbamate.
- Use of weight loss agents or drugs known to affect appetite (including glucagon-like peptide-1[GLP-1] analogs).
- Any other investigational drug or investigational device.
- Medication that are strong inhibitors/inducers/ sensitive substrates with a narrow therapeutic index for P450 3A4 (CYP3A4), CYP2D6, CYP3A4, or CYP2D6.

Although they are not prohibited, patients taking concomitant medications may require that the patient is monitored with special care to identify any AEs arising due to the potential for altered drug metabolism.

4.8. Treatment After the End of Study

After the Safety Period, patients will have their taper schedule initiated over a 3-6 day period (see Section 3.1.2).

5. STUDY DRUG MATERIALS AND MANAGEMENT

5.1. Labeling and Packaging

5.1.1. Labeling

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

5.1.2. Packaging

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

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

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

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

5.2. Dispensing and Storage

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

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

The DEA regulations detail specific security requirements for storage of the investigational product. Licensed practitioners must store controlled substances in a “securely locked, substantially constructed cabinet” and must notify the DEA of the theft or significant loss of any controlled substances within one business day of discovering such loss or theft. Furthermore, all practitioners are prohibited from hiring employees who have been convicted of a drug-related felony or who have had a DEA registration denied or revoked.

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

Doses of Cannabidiol Oral Solution will be administered from the Schedule I-licensed study center.

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

5.3. Drug Supply and Accountability

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

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

If the study is terminated, discontinued, suspended, or completed, all unused supplies of the investigational product may be destroyed via the use of a third-party vendor or be returned to the Sponsor or a designee after the final drug accountability check has been performed. A certificate of destruction will be provided to the Sponsor.

All regulations issued by the DEA concerning the accountability of Schedule I medications will be followed (e.g., prevention of diversion).

6. STUDY ASSESSMENTS

6.1. Safety Assessments

For all patients physical examination, vital signs (seated blood pressure, pulse rate, temperature, and respiration rate), clinical laboratory testing (hematology, chemistry, and urinalysis), 12-lead ECG, concomitant medication, C-SSRS, and AE assessments (including TEAEs and SAEs).

6.1.1. Physical Examinations

A physical examination (evaluation of general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities) will be conducted for every patient during the Visit 1 (Day 1), all monthly and quarterly visits, and Visit 7 (End of Study) or Early Withdrawal.

6.1.2. Vital Signs

Vital signs (seated blood pressure, pulse rate, temperature and respiration rate) will be measured during Visit 1 (Day 1), all monthly & quarterly visits, and Visit 7 (End of Study) or Early Withdrawal. Additional vital sign measurements may be performed as deemed medically necessary by research personnel.

6.1.3. Electrocardiograms

A resting 12-lead ECG will be conducted during Visit 1 (Day 1), all monthly & quarterly visits, and Visit 7 (End of Study) or Early Withdrawal.

6.1.4. Clinical Laboratory Assessments

Blood samples for hematology and chemistry assessments and urine sample for urinalysis will be collected during Visit 1 (Day 1), all monthly & quarterly visits, and Visit 7 (End of Study) or Early Withdrawal.

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, red blood cell (RBC), and platelet count.
- Chemistry: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na^+), potassium (K^+), chloride (Cl^-), lactate dehydrogenase (LDH), uric acid, glucose, and calcium.
- Urinalysis (Visit 1 and Visit 7 or Early Withdrawal only): pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range a microscopic examination will be performed.

A urine drug screen (amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol) will be performed during at Visit 1 and Visit 7 (End of Study) or Early Withdrawal.

A urine dipstick pregnancy test will be performed on all female post-menarchal patients during at Visit 1 and Visit 7 (End of Study) or Early Withdrawal.

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

The C-SSRS is a prospective assessment tool routinely used in studies of drugs with any potential for CNS effects. It captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The questionnaire will be completed during Visit 1 (Day 1) and at the end of the Safety Period (Visit 7) or Early Withdrawal Visit.

Patients who have significant findings for suicidal ideation as assessed by the C-SSRS must be referred to the investigator for follow-up evaluation.

6.1.6. Concomitant Medications

Will be assessed at all visits.

6.1.7. Adverse Events and Serious Adverse Events

6.1.7.1. Definition of Adverse Events

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

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

An AE may be:

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

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

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

Patients will be monitored throughout the study for AEs. All AEs must be followed until they are resolved or stabilized, or until all attempts to determine resolution of the event are exhausted.

The investigator should use his/her discretion in ordering additional tests as necessary to monitor the progress of such events.

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

6.1.7.2. Classification of Adverse Events

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

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

6.1.7.3. Causality/Drug Relationship Assessment

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

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

6.1.7.4. Definition of Serious Adverse Events

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

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

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

6.1.7.5. Actions Taken

Actions taken may consist of:

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

6.1.7.6. Outcome at the Time of Last Observation

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

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

6.1.7.7. Adverse Event Recording and Reporting

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

Expedited reporting is required for serious unexpected adverse drug reactions. Fatal or life-threatening unexpected drug reactions must be reported by the Sponsor to regulatory agencies no more than 7 days after the Sponsor's first knowledge of the reaction; followed by as complete a report as possible within 8 additional days. Unexpected drug reactions must be

reported no later than 15 days after the Sponsor's first knowledge of the reaction. In order to comply with these requirements, the investigator or delegate must inform the Sponsor immediately upon occurrence of any SAE. The site will complete the SAE Report Form as thoroughly as possible and e-mail it to Insys within 24 hours of the investigators first knowledge of the event.

Sponsor contact information is listed below:

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

These SAE reports must contain the following information:

A. Study name/number

B. Study drug

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

D. Patient number

E. Patient initials

F. Patient demographics

G. Clinical event

   1) Description

   2) Date of onset

   3) Treatment (drug, dose, dosage form)

   4) Adverse event relationship to study drug

   5) Action taken regarding study drug in direct relationship to the AE

H. If the AE was fatal or life-threatening

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

J. Autopsy findings (if available)

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

6.1.7.8. Adverse Event Follow-Up

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

6.1.7.9. Special Considerations

Cannabidiol inhibits drug metabolism mediated by a subset of CYP proteins (see Section Section 1.1.2). Thus, the investigator and study center staff should monitor patients who are taking concomitant medications that are metabolized by CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP1A2, or by P-glycoprotein with special care.

6.2. Efficacy Assessment

The HQ-CT will be completed at the Study Completion/Early Withdrawal. The questionnaire assesses food-related problem behaviors and consists of three factors: Hyperphagic Drive (internal consistency 0.76), Hyperphagic Behavior (internal consistency 0.80) and Hyperphagic Severity (internal consistency 0.60). It is a 13-item parent completed questionnaire (Fehnel et al., 2015).

7. STUDY PROCEDURES

Prior to performing any study related procedures or assessments, the Investigator will ensure that the patients and/or their parent(s)/caregiver(s) (if applicable) provide written informed consent and that the perdiatric patient provides assent (as appropriate). Patients and their parent(s)/caregiver(s) (if applicable) will receive a copy of the informed consent form (ICF) and asent 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 11.4 for guidelines regarding patient consent and assent.

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

7.1. Safety Period

7.1.1. Visit 1 (Day 1)

The following procedures and assessments will be performed:

- Obtain written informed consent/assent (if appropriate).
- Review of inclusion and exclusion assessment.
- Review/assess concomitant medications.
- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Collect blood samples for clinical labs (chemistry and hematology)
- Collect urine sample for urinalysis, urine drug screen, and urine dipstick pregnancy test (all female patients of childbearing potential).
- Perform resting 12-lead ECG.
- Perform physical examinations.
- Record weight.
- Dispense CBD.
- Perform drug accountability.
- Review AEs.

7.1.2. Monthly (Visits 2, 3, and 4) and Quarterly (Visits 5, and 6) Visits

The following procedures and assessments will be performed:

- Review/assess concomitant medications.
- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Collect blood samples for clinical labs (chemistry and hematology)
- Perform resting 12-lead ECG.

- Perform physical examinations.
- Record weight.
- Collect/review/dispense CBD.
- Perform drug accountability.
- Review AEs.

7.2. End of Study (Visit 7) or Early Withdrawal

The following procedures and assessments will be performed:

- Review/assess concomitant medications.
- Record vital signs (seated blood pressure, pulse rate, temperature, and respiration rate).
- Collect blood samples for clinical labs (chemistry and hematology)
- Collect urine sample for urinalysis, urine drug screen, and urine dipstick pregnancy test (all female patients of childbearing potential).
- Perform resting 12-lead ECG.
- Perform physical examinations.
- Record weight.
- Complete the HQ-CT.
- Collect/review CBD.
- Perform drug accountability.
- Review AEs.
- Dispense CBD for Taper Period.

End of Study assessments (If the patient withdraws prematurely from the Safety Period, all Visit 7 (End of Study) procedures should be conducted. Site staff will follow-up with the patient 4 weeks after completion of study via the telephone to collect information regarding AEs and concomitant medications.

7.3. Taper Period (Visit 8)

The following procedures and assessments will be performed:

- Collect CBD.
- Review concomitant medication and AEs.

7.4. Follow-Up Period (Visit 9)

The following assessments will be performed by phone call 30 days after Visit 7 (End of Study):

- Review/assess concomitant medications and review AEs.

8. STATISTICS

8.1. Safety Endpoints

Changes in safety endpoints will be reported as mean/median change from baseline at relevant time points and as a listing of events that fall outside normal limits. Baseline is defined as Visit 10 of INS011-16-085.

- Incidence, type, and severity of AEs and serious adverse events (SAEs) associated with Cannabidiol Oral Solution (i.e., treatment-emergent adverse events [TEAEs]).
- Changes from baseline in vital signs, physical exam, ECG findings, and laboratory values (hematology, chemistry, and urinalysis).
- Change from baseline in weight.

8.2. Efficacy Endpoint

- Change in the total score of the HQ-CT from Baseline to Study Completion/Early Withdrawal.

Details of the exploratory analysis of this endpoint will be provided in the Statistical Analysis Plan.

8.3. Sample Size Determination

The sample size is based on successful completion of INS011-16-085, with a maximum of 66 patients.

8.4. Analysis Populations

Statistical analsysis will be conducted on all enrolled patients.

8.5. Statistical Analyses

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

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

8.5.1. Study Patients and Demographics

8.5.1.1. Disposition and Withdrawals

The numbers of patients entering, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall and by modal dose group. For each patient, the modal dose is the dose with the longest exposure during the study.

8.5.1.2. Protocol Deviations

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

8.5.1.3. Demographics and Other Baseline Characteristics

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

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

8.5.2. Exposure and Compliance

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

8.5.3. Safety and Tolerability Analyses

No formal inferential analyses will be conducted for safety variables. Data listings will be provided for protocol-specified safety data.

8.5.3.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA, version 20.0 or higher) will be used to classify all AEs. Adverse event summaries will include only TEAEs, which will be summarized for each modal dose group. For each patient, the modal dose is the dose with the longest exposure during the study.

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

8.5.3.2. Clinical Laboratory Evaluations

For the continuous laboratory parameters, descriptive statistics will be presented for values collected at all study visits as indicated in Table 1.

8.5.3.3. Vital Signs

For blood pressure, pulse rate, temperature, and respiration rate, descriptive statistics will be presented for values collected at all study visits as indicated in Table 1.

8.5.3.4. Electrocardiograms

For the continuous ECG parameters, descriptive statistics will be presented for values collected at all study visits, and for the changes from Baseline to End of Study/Early Withdrawal.

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

8.5.3.5. Physical Examination Findings

Physical examination body systems will be presented as the number and percentage of patients that have normal or abnormal results at each visit. The examination will include evaluation of height, weight, general appearance, skin, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities.

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

C-SSRS categorization based on Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories 1, 2, 3, 4, and 7 will be summarized as dichotomous endpoints at Visit 1 (Day 1) and End of Study/Early Withdrawal Visits.

8.5.4. Interim Analysis

No interim analyses are planned.

8.5.5. Missing Data

There will be no imputation of the missing values. All assessments will be conducted based on all the observed data.

9. STUDY CONDUCT

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

9.1. Sponsor and Investigator Responsibilities

9.1.1. Sponsor Responsibilities

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

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

9.1.2. Investigator Responsibilities

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

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

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

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

9.2. Site Initiation

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

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

9.3. Screen Failures

Patients who fail inclusion and/or exclusion criteria may not be rescreened for the study.

9.4. Study Documents

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

9.4.1. Investigator's Regulatory Documents

The regulatory documents must be received from the investigator and reviewed and approved by the sponsor or sponsor's representative before the study site can initiate the study and before the sponsor, or sponsor's representative, will authorize shipment of investigational product (IP) to the study site. Copies of the investigator's regulatory documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the IB, CRF/electronic case report form (eCRF) completion guidelines, copies of regulatory references, copies of IRB correspondence, and IP accountability records should also be retained as part of the investigator's regulatory documents. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

9.4.2. Case Report Forms

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

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

To ensure data accuracy, CRF/eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the CRF/electronic

data capture (EDC) system according to the completion guidelines provided by the sponsor, or sponsor's representative.

9.4.3. Source Documents

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

During the study, select CRF/eCRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or the sponsor's representative. A paper copy of the laboratory results will be provided to the study site and should be retained with each patient's source data.

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

9.5. Study Termination

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

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

9.6. Study Site Closure

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

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

9.6.1. Record Retention

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

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

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

9.6.2. Laboratory Sample Retention

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

10.1. Changes To The Protocol

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

10.2. Monitoring

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

10.3. Data Review Meeting

The sponsor will review all data reported in CRFs of all patients before database lock. The data review meeting determines whether all enrolled patients can be included in the analysis population according to the specified definition of analysis populations and evaluates whether or not medical decisions of the investigator were appropriate for important data affecting the safety endpoints.

10.4. Protocol Violations

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

The investigator or sub-investigator should document any deviation from the protocol and the reason. If the investigator performs a deviation from the protocol or a change of the protocol to

eliminate an immediate hazard(s) to patients, the record should be immediately submitted to the sponsor, the CRU, and the IRB by the investigator and the IRB will provide expedited review and approval. After the investigator has obtained approval of the IRB, the investigator should obtain written permission of the CRU and written agreement of the sponsor.

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

10.5. Quality Assurance Audit

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

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

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

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

11. REGULATORY AND ETHICAL CONSIDERATIONS

11.1. Regulatory Authority Approval

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

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

11.2. Ethical Conduct of the Study

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

11.3. Statement of Investigator/Delegation of Authority

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

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

11.4. Patient Informed Consent

The investigator or his/her designee will inform the patient of all aspects pertaining to their participation in the study. The process for obtaining patient informed consent will be in accordance with all applicable regulatory requirements (e.g., CFR Part 50 and ICH E6 Section 4.8). The investigator or his/her designee and the patient must both sign and date the informed consent document (ICD) before they can participate in the study. The patient will receive a copy of the signed and dated form, and the original will be retained in the site's study records. The decision to participate in the study that is made by the patient is entirely voluntary. The

investigator or his/her designee must emphasize to the patient that consent for study participation may be withdrawn at any time without penalty or loss of benefits to which the patient is otherwise entitled. If the ICD is amended during the study the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICD by the IRB, and use of the amended form, including the necessity of re-consenting ongoing patients.

11.4.1. Assent Guidance

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 patients (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 patients 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 patients in this study will not be required. Informed consent from all parent(s)/caregiver(s) will be required.

11.5. Investigator Reporting Requirements

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

12. DATA HANDLING AND RECORD KEEPING

The Contract Research Organization (CRO) will be responsible for data management and analysis. The procedures will be specified in the Data Management Plan.

12.1. Data Management

The CRO will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the CRO's standard operating procedures (SOPs). A comprehensive Data Management Plan will be developed including a data management overview, database contents, annotated CRF and consistency checks. Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

12.2. Case Report Forms and Source Documents

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

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

12.3. Documentation and Retention of Essential Documents

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

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

12.4. Financial Disclosure

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

The US FDA Financial Disclosure by Clinical Investigators (21 Code of Federal Regulations [CFR] 54) regulations require sponsors to obtain certain financial information from investigators participating in covered clinical studies; each investigator and sub-investigator is required to provide the required financial information and to promptly update Insys Development Company, Inc., with any relevant changes to their financial information throughout the course of the clinical

study and for up to one year after its completion. This rule applies to all investigators and sub-investigators participating in covered clinical studies to be submitted to the FDA in support of an application for market approval.

13. FACILITIES

Selection of specific study vendors is pending.

14. USE OF INFORMATION AND PUBLICATION POLICY

14.1. Use of Information

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

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

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

14.2. Publication Policy

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

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16. INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Open-Label Study to Assess the Long-Term Safety of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Patients with Prader-Willi Syndrome

PROTOCOL NO: INS011-17-115

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.

1) I have received and reviewed the Investigator's Brochure for Cannabidiol Oral Solution.
2) I agree to conduct the study outlined above according to the terms and conditions of the Protocol INS011-17-115, GCP guidelines, and with applicable regulatory requirements.
3) I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
4) I agree to permit representatives of Insys Development Company, Inc. and their designated representatives to perform trial-related monitoring and auditing, including auditing of the IRB and regulatory documents, by providing direct access to all source data and documents.

Signature of Investigator: _____

Printed Name: _____

Date: _____

Investigator Title: _____

Address: _____