# Statistical Analysis Plan

## 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: 04 Oct 2018
Version: 1.0
Investigational Product: Cannabidiol Oral Solution
IND Number: IND 136,374

ClinicalTrials.gov ID: NCT03458416

# Statistical Analysis Plan

## Insys Development Company, Inc.

## Protocol No.: INS011-17-115

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



Covance Study ID: 000000163385
Document Version: Final 1.0
Document Date: 04 Oct 2018

**Covance Inc. CDCS**
**Clinical Development Commercialization Services**

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# Approvals

*The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.*

***Approved by***
***Covance Lead Statistician Approval***

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Signature 04OCT2018 Date

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Signature 10 OCT 2018 Date

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# Reviewers

The following reviews of the SAP were conducted:

| Name and Title | Role | Version Last Reviewed | Company/ Organization |
|---|---|---|---|
| PPD | Peer Review Statistician | Internal draft 1.0 | Covance |
| | Lead Programmer | Internal draft 1.0 | Covance |
| | Project Manager / Clinical Team Lead | Internal draft 1.0 | Covance |
| | Project Physician | Internal draft 1.0 | Covance |
| | Client Approver | Sponsor draft 2.0 | Insys |
| | Client Approver | Sponsor draft 2.0 | Insys |
| | Client Approver | Sponsor draft 2.0 | Insys |

# Version History

| Version # | Description of Changes | Version Date |
|---|---|---|
| Final 1.0 | 4 October 2018 | |

# Glossary of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CBD | Cannabidiol Oral Solution |
| C-CASA | Columbia Classification Algorithm of Suicide Assessment |
| CI | Confidence Interval |
| CRF | Case Report form |
| eCRF | Electronic Case Report Form |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| ECG | Electrocardiogram |
| HQ-CT | Hyperphagia Questionnaire for Clinical Trials |
| HR | Heart Rate |
| IMP | Investigational Medicinal Product |
| MedDRA | Medical Dictionary for Regulatory Activities |
| LS | Least Squares |
| PT | Preferred Term |
| PWS | Prader-Willi Syndrome |
| QTcF | Fridericia corrected QT interval |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| TESAE | Treatment Emergent Serious Adverse Event |
| TFLs | Tables, Figures and Listings |

# 1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

| Document | Date | Version |
|---|---|---|
| Protocol | 27 February 2018 | 1.0 |
| eCRF | 25 July 2018 | 1.0 |

# 2. Protocol Details

## 2.1 Study Objectives

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 (PWS).

## 2.2 Overall Study Design

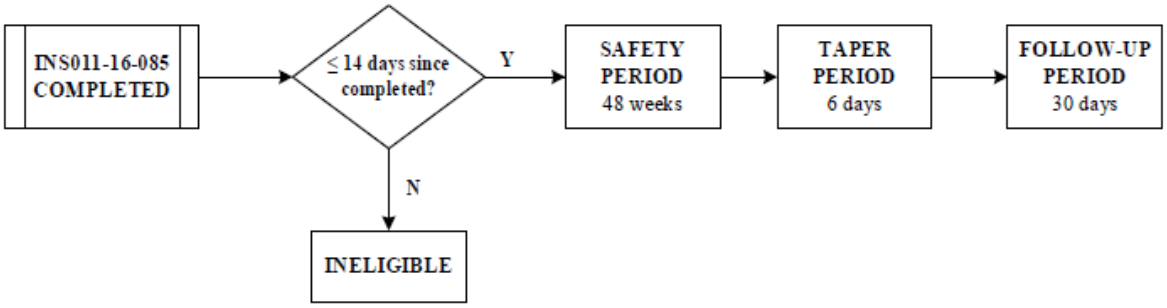
This is a multicenter, open-label study designed to assess long-term safety and tolerability of CBD in patients with PWS. Patients must have completed INS011-16-085 to be eligible for this study.

Patients may enroll in this long-term safety study after completing INS011-16-085 Visit 10 (Study Completion) to avoid interruption of the investigational medicinal product (IMP). Patients will have up to 2 weeks to enroll in INS011-17-115. If a patient does not enroll within the 2-week window, they will not be eligible to enroll into the study.

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. Patients may have their dose of study medication adjusted down once from 40 mg/kg/day to 30 mg/kg/day or from 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.

The study consists of a Safety Period (48 ± 2 weeks), Taper Period (6 ± 3 days), and a Follow-up Period (30 ± 5 days).

The study design is presented in Figure 1.




All screening, efficacy and safety evaluations will be performed according to the schedule of assessments presented in Appendix A.

### 2.3 Sample Size and Power

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

## 3. Efficacy and Safety Variables

### 3.1 Safety Endpoints

The safety endpoints for this study are:

- Incidence, type and severity of adverse events (AEs) and serious adverse events (SAEs) associated with CBD, 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

### 3.2 Efficacy Endpoint

The efficacy endpoint for this study is the change in total score of the hyperphagia questionnaire for clinical trials (HQ-CT) from Baseline to Study Completion/Early Withdrawal, where baseline is defined as Visit 10 of INS011-16-085. The HQ-CT is a 9-item questionnaire and the response for each item ranges from 0 (for responses such as "Not at all" or "Never") to 4 (for responses such as "Several times"). The total HQ-CT score is calculated by adding the responses to each item, thereby yielding a total HQ-CT score which can range from 0 to 36 (Fehnel, et al., 2015).

## 4. Analysis populations

### 4.1 All Enrolled Population

All patients enrolled will be included in the all enrolled population.

## 4.2 Special Subpopulations

Not applicable.

# 5. DATA Handling

## 5.1 Time points and Visit Windows

Day 1 is defined as the date of enrollment onto INS011-17-115 study. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

All data will be analyzed using nominal study visits as defined in the Study Schedule (see Appendix A). No visit windows will be applied for summary and analysis.

Multiple visits within the same protocol-defined scheduled window (see Appendix A) will be dealt with as follows:

- If multiple scheduled visits occur within a single protocol-defined visit window then the visit closest to the target day of the visit window will be used in the analysis. In cases where the measurements are equal distances from the target day, the later visit will be used in the analysis.

## 5.2 Handling of Dropouts, Missing Data, and Outliers

There will be no imputation of missing data. All summaries will be based on observed data only.

For adverse events (AEs) with missing or partial start date:

- If the partial onset date does not indicate whether the AE started prior to or after the end of the treatment-emergent period (last dose of double-blind treatment plus 14 days), the AE will be classified as treatment-emergent.
- If the AE onset date is partial or missing, the AE end date will be considered. If the AE end date is partial and the partial end date does not indicate that the AE ended prior to the start of double-blind treatment, the AE will be classified as treatment-emergent.

In the event that a partial date for concomitant medication is available, this partial information will be used as follows:

- If the partial start date does not indicate whether the medication started prior to or after double-blind treatment, the medication will be classified as both prior and concomitant.

- If the partial end date does not indicate that the medication ended prior to the start of double-blind treatment, the medication will be classified as both prior and concomitant.

The imputations for AEs and medications are for categorization purposes only and will not be used in listings.

# 6. Statistical Methods

## 6.1 General Principles

All data processing, summarization and analyses will be performed using Covance's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The analysis treatment group will be defined by the modal dose of study drug (dose of the study drug that the patient took for the longest period).

The following principles will be applied to all TFLs unless otherwise stated:

| Principle | Value |
|---|---|
| Significant tests | Two-sided and use a 5% significance level |
| Treatment group labels and order presented | Listings:<br>Cannabidiol Oral Solution (20mg/kg/day)<br>Cannabidiol Oral Solution (30 mg/kg/day)<br>Cannabidiol Oral Solution (40 mg/kg/day)<br>Tables:<br>CBD (20 mg/kg/day)<br>CBD (30 mg/kg/day)<br>CBD (40 mg/kg/day)<br>All CBD |
| Tables | Data in summary tables presented by treatment group and visit (where applicable) |
| Listings | All data collected presented by<br>Treatment group<br>Patient<br>Visit (where applicable)<br>Date;<br>unless otherwise specified |
| Descriptive summary statistics for continuous variables | Number of patients/observations (n)<br>Mean<br>Standard deviation (SD) |

| Principle | Value |
|---|---|
| | Median<br>Minimum<br>Maximum |
| Descriptive summary statistics for categorical variables | Frequency counts and percentages [n (%)] |
| Denominator for percentages | Number of patients in the analysis population, unless stated otherwise in table shell(s) |
| Include "Missing" as category | Yes, when the number missing is greater than zero for at least one treatment group |
| Display for 0 percentages | Leave blank |
| Display to one more decimal place than collected value | Mean<br>Mean Difference<br>Median<br>Percentages |
| Display to two more decimal places than collected value | Standard Deviation<br>Confidence Interval |
| Limit of precision for displays | 3 decimal places |

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

## 6.2 Subject Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by treatment group and overall and will include the number and percentage of patients:

- Entered Safety Period
- Completed Study
- Entered Taper Period
- Entered Follow-up Period

In addition, the number and percentage of patients who complete the study and who discontinue early, including a breakdown of the primary reasons for discontinuation from the study will be presented.

A summary of patient enrollment by site will also be provided by treatment group and overall for the enrolled population.

A listing of study drug bottle numbers and assignments will be produced.

## 6.3 Protocol Deviations

All important protocol deviations will be listed and summarized by treatment group for the enrolled population.

## 6.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for enrolled population. Standard descriptive statistics will be presented for the continuous variables of:

- age (years) ;
- gender (Male, Female);
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown);
- race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other);
- weight (kg) at Day 1 visit;
- height (cm) at Day 1 Visit;
- body mass index (kg/$m^2$) (derived on eCRF);

No formal tests of statistical significance will be performed on the demographic and baseline data.

Other baseline measurements, such as vital signs and ECG, will be summarized by treatment group with the post-baseline measurements.

### 6.4.1 Medical or Surgical History

Medical or surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 21.1 (or a later version if updated during the study)]. All medical history or surgical history will be listed, and the number and percentage of patients with any medical or surgical history will be summarized for all enrolled population by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

### 6.4.2 Prior and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by Covance using the WHO Drug Dictionary [Version March 2018 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those prior to the first dose date of IMP treatment on INS011-16-085.

Concomitant medications are those with a start date on or after the first dose date of IMP treatment on INS011-16-085, or those with a start date before the first dose date of IMP treatment and a stop date on or after the first dose date of IMP treatment or ongoing end of study.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for enrolled population.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

## 6.5 Measurements of Treatment Compliance

Percentage compliance is calculated based on the study drug administration page as follows:

$$100 \times \frac{\text{\# doses taken}}{\text{Expected \# doses (based on visit days)}},$$

where # doses taken = # of the "yes" responses to "Was AM dose taken?" and "Was PM dose taken?"

Percentage compliance will be summarized descriptively by treatment group for the enrolled population.

The following percentage compliance categories will also be presented:

- <90.0%
- ≥90.0% and ≤110.0%
- >110.0%

In addition, summary statistics of the weights of bottles dispensed and returned, as well as the volume administered, will be presented by treatment group for the enrolled population.

All study drug administration and drug accountability data will be listed in full.

## 6.6 Efficacy

All statistical inference will be based on a comparison of the CBD treatment groups. Descriptive statistics for efficacy endpoints will be based on all treatment groups, i.e. CBD (20 mg/kg/day), CBD (30 mg/kg/day), CBD (40 mg/kg/day), and all CBD.

### 6.6.1 Exploratory Efficacy Analysis

Total HQ-CT scores and changes from baseline will be summarized by treatment group and visit using standard descriptive statistics.

### 6.6.2 Sensitivity Analysis

Not applicable.

### 6.6.3 Secondary Efficacy Analysis

Not applicable.

### 6.6.4 Subgroup Analysis

Not applicable.

### 6.6.5 Columbia Suicide Severity Rating Scale

Responses Columbia Suicide Severity Rating Scale (C-SSRS) will be listed separately for the adult and child-completed assessments. The listings will be based on the enrolled population.

C-SSRS will be categorized based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categories 1, 2, 3, 4 and 7 as follows (Gassmann-Mayer, et al., 2011):

| Event code | C-CASA event | C-SSRS event[a] |
|---|---|---|
| 1 | Suicide completed | Completed suicide |
| 2 | Suicide attempt | Actual attempt |
| 3 | Preparatory actions towards imminent suicidal behaviour (including interrupted attempt or aborted attempt) | Interrupted attempt<br>Aborted attempt<br>Preparatory acts or behavior |
| 4 | Suicidal ideation | Subscale code and event:<br>1. Wish to be dead<br>2. Non-specific active suicidal thoughts<br>3. Active suicidal ideation with any methods (not plan) without intent to act<br>4. Active suicidal ideation with some intent to act, without specific plan<br>5. Active suicidal ideation with any specific plan and intent |
| 7 | Self-injurious behavior | Has the subject engaged in non- |

| | | |
|---|---|---|
| | without suicidal intent | suicidal self-injurious behavior? |

[a]An event corresponds to a "yes" response to the C-SSRS question.

C-SSRS will be summarized as dichotomous endpoints corresponding to the C-CASA categories at Visit 1 and End of Study/Early Withdrawal Visits.

## 6.7 Safety

### 6.7.1 Extent of Exposure

Duration of exposure will be defined in days as:

(date of last dose – date of first dose) + 1.

Duration of exposure will be summarized using descriptive statistics for each treatment group for the enrolled population.

### 6.7.2 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [Version 21.1 (or a later version if updated during the study)] and classified as treatment – emergent AEs (TEAEs) as follows:

- TEAEs are events with start date on or after the date of first dose of IMP and up to 14 days after the last dose of IMP or events with start date prior to the date of first dose of IMP whose severity worsens on or after the date of first dose of IMP on INS011-17-115.

All AE data will be listed by treatment group. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of treatment-emergent serious AEs (TESAEs), AEs leading to permanent discontinuation of IMP and AEs resulting in death will be produced. AE ongoing or worsened from INS011-16-085 will be listed.

Summary tables of TEAEs by treatment group and overall will be produced for the enrolled population. No statistical comparisons of AEs between treatment groups will be performed.

The severity of all AEs is recorded as mild, moderate, or severe. If severity is missing for a TEAE, it will be considered severe.

The relationship between an AE and IMP treatment is assessed as definite, probable, possible, unlikely or not related. A treatment-related AE is an AE considered by the investigator as definitely, possibly, or probably related to IMP treatment or with unknown/missing relationship to IMP treatment.

An overview table will summarize the number and percentage of patients with at least one of the following TEAEs, where patients with more than one TEAE in a particular category are counted only once in that category:

- any TEAE;
- TEAE by severity (mild, moderate, severe);
- treatment-related TEAE;
- severe treatment-related TEAE;
- TESAE;
- TESAE by severity;
- treatment-related TESAE;
- TEAE leading to study drug discontinuation.

The overview table will be repeated to summarize the number of TEAEs (displaying the number and percentage of observed events).

The number and percentage of patients reporting each AE will be summarized by System Organ Class (SOC) and Preferred Term (PT) for all enrolled patients. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs, by SOC and PT;
- TEAEs related to IMP treatment, by SOC and PT;
- TEAEs by relationship to IMP treatment, by SOC and PT;
- TEAEs by maximum severity, by SOC and PT;
- TEAEs related to IMP treatment by maximum severity, by SOC and PT;
- TEAEs causing discontinuation from IMP treatment, by SOC and PT;
- TEAEs related to IMP treatment causing discontinuation from IMP treatment, by SOC and PT;
- TESAEs, by SOC and PT;
- TESAEs related to IMP treatment, by SOC and PT;
- TEAEs leading to death, by SOC and PT.

In the above summaries, patients with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one TEAE within a particular PT are counted only once for that PT. For summaries by maximum severity, patients with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing intensity/severity will be included (as severe) in the overall count of patients with TEAEs, but will not be included in the counts of patients with TEAEs within a SOC or PT.

### 6.7.3 Laboratory Evaluations

#### 6.7.3.1 Standard Safety Laboratory Panel

Data for the following hematology, blood chemistry, and urinalysis analytes received from central laboratory will be listed and summarized by treatment group and visit. If data for any additional analytes are also received or recorded, then these will be listed only.

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| Hemoglobin | Albumin | pH |
| Hematocrit | Blood Urea Nitrogen | Specific Gravity |
| Total Leukocyte Count | Creatinine | Protein |
| Differential Leukocyte Count | Total Bilirubin | Glucose |
| Red Blood Cell Count | Alkaline Phosphatase (ALP) | Ketones |
| Platelets | Aspartate Transaminase (AST) | Bilirubin |
| Neutrophils (abs, %) | Alanine Transaminase (ALT) | Blood |
| Lymphocytes (abs, %) | Sodium | Nitrite |
| Monocytes (abs, %) | Potassium | Leukocyte Esterase |
| Eosinophils (abs, %) | Chloride | Urobilinogen |
| Basophils (abs, %) | Lactate Dehydrogenase (LDH) | Color and Clarity |
| White Blood Count | Uric Acid | Microscopic |
| | Glucose | Urine T. Protein, Random |
| | Calcium | Urine Creatinine, Random |



All laboratory data will be reported in conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">"sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory and urinalysis data will be summarized by visit using standard descriptive statistics for the enrolled population. Changes from baseline will also be summarized.

For hematology and serum chemistry, shift tables presenting movement in and out of reference ranges from baseline to each scheduled post-baseline visit will be

provided for each treatment group. Corresponding shift tables will be produced for urinalysis.

#### 6.7.3.2 Urine Drug Screen

A urine sample for the following assessments will be collected at study entry and end of study/early withdrawal: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine and tetrahydrocannabinol.

Results from the urine drug screen will be listed for the enrolled population.

#### 6.7.3.3 Urine Pregnancy Test

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

Pregnancy screen results will be listed for the enrolled population.

### 6.7.4 Vital Signs

The following vital signs will be listed and summarized by treatment group and visit.

- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- pulse rate (bpm);
- body temperature (°C);
- respiratory rate (breaths/min);
- weight (kg)
- height (m)
- BMI ($kg/m^2$).

Vital signs data and changes from baseline in vital signs will be summarized by visit using standard descriptive statistics for the enrolled population. Shift tables will also be presented from baseline to outside normal range criteria.

All vital sign data collected for the enrolled population will be listed.

### 6.7.5 Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- Heart rate (bpm);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);

- QTcF interval (msec)
- RR interval (msec).

An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant").

The ECG measurements and changes from baseline in ECG will be listed and summarized by treatment group and visit using standard descriptive statistics for the enrolled population.

The Investigator assessment will be listed and the number and percentage of patients within each assessment category will be tabulated by treatment group and visit for the enrolled population. Shifts from baseline at each post-baseline visit will be presented.

A listing of ECG measurements and findings will be produced for all enrolled patients.

### 6.7.6 Physical Examination

Physical examination results (normal/abnormal) and details of abnormalities (Abnormal, Not Clinically Significant and Abnormal, Clinically Significant) will be listed for all enrolled patients.

For each physical examination body system, the number and percentage of patients with abnormalities at baseline and post-baseline will be summarized by treatment group for the All Enrolled Population. Shifts from baseline according to normal and abnormal criteria will also be presented for all patients

## 6.8 Interim Analysis

No interim analysis will be performed for this study.

# 7. Changes in Planned Analysis

Not applicable.

# 8. Data Issues

Not applicable.

# 9. References

Fehnel, S., Brown, T. M., Nelson, L., Chen, A., Roof, E., Kim, D. D., et al. (2015). Development of the hyperphagia questionnaire for use in Prader-Willi syndrome clinical trials. *Presented at ISPOR 20th Annual International Meeting.*

Gassmann-Mayer, C., Jiang, K., McSorley, P., Arani, R., DuBrava, S., Suryawanshi, S., et al. (2011). Clinical and statistical assessment of suicidal ideation and behavior in pharmaceutical trials. *Clinical Pharmacology and Therapeutics, 90*(4), 554-560.

# Appendix A: 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 |

**Statistical Analysis Plan**

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-17-115 Covance Study ID: 000000163385

| 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.