### 16.1.9 Documentation of Statistical Methods

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| Statistical Analysis Plan | 04 April 2017 |
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# STATISTICAL ANALYSIS PLAN

## INS011-14-030 / NCT02318602

## A MULTICENTER, OPEN-LABEL, FLEXIBLE DOSE STUDY TO ASSESS THE LONG-TERM SAFETY OF PHARMACEUTICAL CANNABIDIOL ORAL SOLUTION AS AN ADJUNCTIVE TREATMENT FOR PEDIATRIC SUBJECTS WITH A TREATMENT-RESISTANT SEIZURE DISORDER WHO COMPLETE INS011-14-029 OR PART A OF INS011-15-054

**AUTHOR:** [redacted]

**VERSION NUMBER AND DATE:** FINAL V1.0, 04APR2017

## STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final v1.0 (Dated 04APR2017) for Protocol INS011-14-030 V5.0 (Dated 06MAR2017).

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| ACS | Abnormal, clinically significant |
| AE | adverse event |
| AED | antiepileptic drug |
| ALT | alanine aminotransferase |
| ANCS | Abnormal, not clinically significant |
| AST | aspartate aminotransferase |
| β-hCG | β human chorionic gonadotropin |
| BLQ | Below the lower limit of quantification |
| BUN | blood urea nitrogen |
| CBD | Cannabidiol |
| CGI-I | Clinical Global Impression of Improvement |
| CGI-S | Clinical Global Impression of Severity |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CTC | Common toxicity grading |
| CTMS | Clinical trial management system |
| DMC | Data monitoring committee |
| DS | Dravet syndrome |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ENR | Enrolled population |
| FSH | follicle-stimulating hormone |
| GGT | gamma glutamyl transferase |
| IP | Investigational product |
| IPES | Impact of Pediatric Epilepsy Scale |
| IS | infantile spasms |
| LFT | liver function test |
| LGS | Lennox-Gastaut Syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OH | hydroxy |
| PK | pharmacokinetics |
| PRO | patient reported outcome |
| PT | preferred term |
| RBCs | red blood cells |
| SAE | serious adverse event |
| SAF | Safety population |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| ULQ | Above the upper limit of quantification |

| | |
|---|---|
| VABS | Vineland Adaptive Behavior Scale, Second Edition – Survey Interview Form including the Maladaptive Behavior Index |
| WBCs | white blood cells |
| WHO-DD | World Health Organization's Drug-Dictionary |

# 1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, plasma level, and safety data for Protocol INS011-14-030. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 5.0, dated October 5, 2016. Protocol INS011-14-030 is a 48-week, phase 3b extension study of Protocols INS011-14-029 and INS011-15-054 Part A.

# 2. STUDY OBJECTIVES

## 2.1. PRIMARY OBJECTIVE

- The primary objective is to assess the long-term safety of Cannabidiol (CBD) Oral Solution as an adjunctive treatment for subjects with treatment-resistant seizure disorders, including Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) or infantile spasms (IS).

## 2.2. SECONDARY OBJECTIVES

The secondary objectives are:

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

# 3. STUDY DESIGN

## 3.1. GENERAL DESCRIPTION

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

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

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

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

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

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

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

Subjects will receive twice daily oral doses of Cannabidiol Oral Solution for approximately 48 weeks or until the IP is successfully approved for marketing in the US (whichever occurs earlier), inclusive of their treatment on the previous study. For subjects that completed INS011-14-029, 48 weeks of treatment would be completed under this protocol. For subjects that participated in INS011-15-054, duration of treatment in INS011-14-030 will be based on the length of time they were enrolled in INS011-15-054 such that total duration of treatment in both studies combined will not exceed approximately 48 weeks. Subjects visit entry into INS011-14-030 will be determined at the discretion of the sponsor and the investigator. All subjects will complete the Final Visit/Discontinuation Visit regardless of when they stop treatment/complete the study. A Follow-up Visit will occur 2 weeks after the Final Visit/Discontinuation Visit.

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

## 3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 3.3 and Table 1 of the protocol.

## 3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Given that an Investigator may choose to down-titrate or up-titrate subjects to any dose, results will not be analyzed and presented "by dose and overall" as currently stated in the protocol. It has been agreed with Insys (13Oct2016) that summaries will only be presented by age category and overall as described in this SAP (Sections 9 to 17).

# 4. PLANNED ANALYSES

The following analysis will be performed for this study:

- Final Safety and Efficacy Analysis
- An Interim analysis may be conducted if deemed necessary.

## 4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study.

## 4.2. INTERIM ANALYSIS

There are no planned interim analyses for this study which require statistical support. Data management will be providing Insys with listings periodically for safety reviews.

## 4.3. FINAL ANALYSIS

The final, planned analysis identified in this SAP will be performed by [redacted] Biostatistics following Database Lock.

# 5. ANALYSIS POPULATIONS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the database lock of the study.

## 5.1. ALL SUBJECTS ENROLLED POPULATION

The enrolled population (ENR) will contain all subjects who signed an informed consent form for this study.

## 5.2. SAFETY ANALYSIS POPULATION

The safety analysis population (SAF) will contain all subjects in the ENR set who received at least one dose of study medication. This is an open-label extension study, so all patients are assigned to receive study medication.

If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis.

All safety and efficacy analyses will be performed on the SAF population.

# 6. GENERAL CONSIDERATIONS

## 6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

## 6.2. BASELINE

For this study, subjects will have 2 different baselines defined as follows:

- The first one (Baseline 1) will be the same as that defined in their previous study. This baseline was defines in the 029 as "baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered prior to baseline. However, AEs and medications commencing on the reference start date will be considered post baseline, unless the start time of the AE is known to be prior to the first dosing of the study medication."
- The second one (Baseline 2) will be the intra-study baseline, defined as the last non-missing measurement prior to the first dose including pre-dose assessments performed on the reference start date. The intra-study baseline could correspond to:
    - Last assessment from the previous study (e.g. Day 11 for subjects from INS011-14-029)
    - Screening (Visit 1) assessment of INS011-14-030
    - Data collected at Day 1 (Visit 2) of INS011-14-030

## 6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/ worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

If the retest measurement occurs prior to the dosing of the first study medication, the retest measurement will be used in the summary statistics if it is the last measurement taken prior to the dose. The retest measurements will not be used in summary statistics for post dose measurements.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

## 6.4. WINDOWING CONVENTIONS

For seizure data only, as the date only is collected on the Subject Diary - Seizure eCRF page, the time points will be assigned to each record considering the following visit windowing:

**Table A: Study Day Windows**

| Assigned Study Day (Inclusive) | | Target Day | Week Assigned |
|---|---|---|---|
| From | To | | |
| -14 | -1 | N/A | Screening |
| 1 | 1 | 1 | Day 1 |
| 4 | 10 | 7 | Week 1 |
| 11 | 17 | 14 | Week 2 |
| 21 | 35 | 28 | Week 4 |
| 49 | 63 | 56 | Week 8 |
| 77 | 91 | 84 | Week 12 |
| 158 | 178 | 168 | Week 24 |
| 242 | 262 | 252 | Week 36 |

For the final visit/discontinuation visit, the date should match with the last record from Seizure Diary eCRF page.

No other visit windowing of scheduled time points will be performed for this study. Data will be summarized based on the planned visit schedule.

## 6.5. STATISTICAL TESTS

No statistical inferential procedures will be performed for this study.

## 6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

## 6.7. SOFTWARE VERSION

All safety and efficacy analyses will be conducted using SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina).

# 7. STATISTICAL CONSIDERATIONS

## 7.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers within the United States. Center pooling will not be carried out for use in analyses for this study.

## 7.2. MISSING DATA

For safety and efficacy analyses, observed values will be used and no imputation will be made for missing data.

Missing dates for Adverse Events (AEs) and concomitant medications will be imputed using the rule provided in Appendix 1. If the intensity is missing for any AE, its intensity will be classified as Severe in the summary tables. If the assessment of relationship of the AE to study treatment is missing, it will be classified as Related in the frequency table of possible related treatment emergent AEs.

## 7.3. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment for multiplicity will be performed since the analyses of safety and efficacy endpoints are descriptive.

## 7.4. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

However analyses will be displayed by age category as follows:

- Infants = 1 to <2 years of age
- Children = 2 to <12 years of age
- Adolescents = 12 to ≤17 years of age

Age categories are based on the subject's age at the beginning of their previous study.

In addition, some relevant results observed during the follow-up period (between the Final visit and the Follow-up visit) or assessed at the Follow-up visit will be presented by CBD status (i.e. subjects who continue to receive CBD after their Final visit versus those who stop receiving CBD after their Final visit). Such analyses are further described in the following sections.

## 8. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted] Biostatistics.

## 9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals, and protocol violations, including inclusion and exclusion criteria will be presented for the ENR set.

The table will summarize the following information:

- Number of subjects screened
- Number of screen failures - overall and by following reasons:
    - subject did not meet eligibility criteria
    - Withdrew informed consent
    - Subject died
    - Other
- Number of treated subjects (SAF)
- Number of subjects in the PK
- Number of subjects who completed study including follow-up
- Number of subjects who discontinued from treatment (overall and by reasons)
- Number of subjects with early discontinuation from study (overall and by reasons)

For both discontinuation from treatment/study the reasons are as follows:

- Inadvertently enrolled (enrollment criteria not met)

- Investigator decision
- Adverse Event
- Subject withdrew consent
- Lack of protocol compliance
- Subject attempted suicide or is at risk of suicide
- Sponsor decision
- Subject becomes pregnant
- Abnormal laboratory values
- Lost to follow-up
- Death
- Other

The following important (clinically) protocol deviations, as identified in the clinical trial management system (CTMS), will be summarized:

- Administrative Criteria
- Eligibility and Entry Criteria
- IP Compliance
- Informed Consent
- Laboratory Assessment Criteria
- Serious AE Criteria
- Study Procedures Criteria
- Regulatory or Ethics Approvals Criteria
- Visit Scheduled Criteria
- Other Criteria

Supportive listings will also be provided:

- Allocation to treatment
- Protocol deviations
- Subjects eligibility criteria

# 10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAF by age category and overall.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Gender
- Race
- Ethnicity
- Weight (kg)
- Height (cm)

For height and weight, the baseline value of the previous study will be reported for subjects who were enrolled no later than 14 days after they completed their previous study. Otherwise, height and weight will be from the screening physical examinations for this study.

### 10.1. DERIVATIONS

- Age (years) = integer portion [(calculated relative to date of signed informed consent – date of birth)/365.25]

## 11. SURGICAL AND MEDICAL HISTORY

Past and current surgical and medical history, as recorded on the *Medical and Surgical History* eCRF page, will be summarized by age category and overall using the System Organ Class (SOC) and Preferred Term (PT) as coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Past medical and surgical conditions are those which stop prior to the first dose of study medication. If both a past and current (ongoing) medical condition records are indicated for a condition, the condition will be presented under current medical conditions only.

A supportive listing will also be provided.

## 12. PRIOR AND CONCOMITANT PROCEDURES

Prior and concomitant procedures, as collected on the *Concomitant Procedure* eCRF page, will be summarized for the SAF, by age category and overall. They will be presented by PT and coded using the latest version of MedDRA.

- 'Prior' procedures are procedures which started and stopped prior to the first dose of study medication.
- 'Concomitant' procedures are procedures which:
    - Started prior to, on or after the first dose of study medication and started no later than 6 days following end of study medication (Unless the procedure is related to SAE. In such a case the procedure can start within 30 days after last study visit.),
    - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.
- 'Post' procedures are procedures which started later than 6 days following end of study medication.

Prior and concomitant procedures observed during the Follow-up period will also be summarized by CBD status.

Prior and concomitant procedures will also be listed.

# 13. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications, as collected on the *Concomitant Medication* eCRF page, will be summarized for the SAF, by age category and overall. They will be presented by PT and coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD).

See Appendix 1 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case (i.e. concomitant).

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which:
  - started prior to, on or after the first dose of study medication and started no later than 6 days following end of study medication,
  - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.
- 'Post' medications are medications which started more than 6 days following the last dose of study medication.

Prior and concomitant medications observed during the Follow-up period will also be summarized by CBD status.

Prior and concomitant medications will also be listed.

In addition, AED medication(s), including stopping or starting medication(s), may be adjusted throughout the trial to maximize seizure control based on tolerability as judged by the investigator. AEDs are recorded on the *Concomitant Medication* eCRF page where the "Reason for medication" is ticked "Antiepileptic drug (AED)".

Changes in AED medication(s) will be analyzed as follows:

- The number of different AEDs a subject took during the study will be summarized
- A bar chart will present the mean number of seizures versus the number of unique AEDs taken during the study for each age category and overall and by type of seizures (separate graphs for tonic and atonic seizures).
- AEDs will be flagged in the listing for all prior and concomitant medications

As for overall concomitant medications, incidence of AEDs will be summarized for each PTs by age category and overall.

AEDs observed during the Follow-up period will also be summarized by CBD status.

# 14. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the SAF, by age category and overall. The following parameters will be summarized:

- Modal dose (defined as the dose with the longest exposure),
- Total duration of study medication at any dose
- Total duration of each dose
- Number of subjects dosed per time points

The date of first study medication administration will be taken from the *Study Drug Administration* eCRF page. The date of last study medication will be taken from the *End of Treatment* eCRF page. In the case of missing data on these eCRF pages, the *Subject Diary – Study Medication Record* eCRF page will be used in order to determine the first and last date of study medication.

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

The corresponding listing will present first/last dose dates, does the subject complete the treatment duration, reason for end of treatment and duration of exposure (days).

In addition, dose modifications will be summarized by age category and overall in terms of:

- Number of subjects with at least one dose modification (as defined Section 14.1)
- Number of subjects with at least one dose changed
- Number of subjects with at least one dose interrupted
- Number of subjects with dose permanently discontinued
- Number of subjects per reason of dose modification
    - Adverse event
    - Lack of efficacy
    - PK-analysis result
    - Other

If a subject experiences several dose modifications for the same reason, he will be counted only once for this reason. However, in the case a subject experiences several dose modifications due to different reasons, he will be counted once for each reason.

A supportive listing will display all the relevant administration details including data/time/interval of each administration, volume planned/administered, reason if dose not administered and amount of water consumed after dosing.

Exposure data coming from the *Subject Diary – Study Medication Record* eCRF page will also be listed.

### 14.1. DERIVATIONS

The following derivation will be used to calculate the duration of exposure:

- Duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.

A dose modification is defined as any change in dose, dose interruption or dose permanently discontinued.

## 15. STUDY MEDICATION COMPLIANCE

The starting dose of the study medication will be determined by the study previously completed by the subject. Dosing of the study medication may be increased or decreased at any dose based on efficacy and tolerability up to a maximum of 40 mg/kg/day.

Noncompliance is defined as taking <80% or >120% of the study medication during any evaluation period (i.e., visit to visit).

Compliance to study medication will be presented for the SAF.

### 15.1. DERIVATIONS

Compliance to study medication will be based on the volume of medication and calculated as follows:

- ”Per Visit” Compliance to study medication will be calculated as follows:

$$\frac{\text{Sum of administered volumes during the week before Visit X}}{\text{Sum of planned volumes during the week before Visit X}} \times 100$$

The compliance per visit will be summarized and reasons for which dose not administered will be listed. The compliance will be clustered as follows: <50%, [50%; 80%[, [80%; 100%[, [100%; 120%], >120%.

## 16. PHARMACOKINETIC AND EFFICACY OUTCOMES

### 16.1. PHARMACOKINETIC

PK analyses will be described in a separate SAP.

### 16.2. EFFICACY OUTCOMES

Efficacy related data do not represent endpoints for this long-term safety study but they will be recorded and

analyzed in terms of:

- Control of seizures (frequency, duration, and severity of seizures compared to each baseline as defined Section 6.2)
- Qualitative subject status (CGI-S, CGI-I, IPES)

The analysis of efficacy-related data will be performed for the SAF.

No statistical inferential procedures will be performed.

### 16.2.1. SEIZURES-RELATED DATA

In this study, seizure frequency, duration, and severity will be assessed to monitor seizure control achieved by long-term treatment with Cannabidiol Oral Solution. Seizures will be observed and recorded using a patient reported outcome (PRO) instrument (i.e., subject/caregiver diaries). Seizures are collected at week 24, week 36 and final visit and they will be compared to the baseline from the previous study.

#### 16.2.1.1. Seizures-Related Variable(s) & Derivation(s)

The following variables will be used to assess the control of seizures:

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

For tonic and atonic seizures, the number of seizures will be recorded. For other types of seizures, the frequency will be reported by range as follows:

  - None
  - 1 to 5 seizures
  - 6 to 19 seizures
  - 20 to 50 seizures

- > 50 seizures.

- Seizure severity:

The assessment of seizure severity will be recorded by the parent(s)/caregiver(s) in the subject seizure and dosing diary. Seizure severity will be categorized as:

- Mild
- Moderate
- Severe

Overall seizure severity will be captured using the CGI-S as described in Section 16.2.2.

- Seizure duration:

The approximate timing of seizure will be recorded by the parent(s)/caregiver(s) in the subject seizure and dosing diary.

#### 16.2.1.2. Missing Data Methods for Seizures-Related Variable(s)

All data will be evaluated as observed; no imputation method for missing values will be used.

The eCRF includes the following question on each study day: "Did the subject experience any seizures?". If the response to this question is no, it will be assumed that the subject does not have any seizures on that day. If the question is not answered, it will be not assumed that the subject does not have any seizures that day (i.e., it will be assumed that the question is inadvertently not answered).

#### 16.2.1.3. Analysis of Seizures-Related Variable(s)

Seizure-related parameters will be summarized as follows:

- Number of subjects (and corresponding percentage) that experienced, by maximum severity, a tonic and atonic seizure, per time point and age category.
- Descriptive statistics (n, mean, SD, median, minimum, and maximum) of the actual number and duration of tonic and atonic seizures, by time point and age category.
- Descriptive statistics (n, mean, SD, median, minimum, and maximum) of the change from baseline in the number and duration of tonic and atonic seizures, by time point and age category.
- Number of subjects by maximum severity, maximum number of seizures and seizure duration for each other types of seizures by time point and age category.
- For each tonic and atonic seizure type, figures will display:
  - Number of seizures per subjects over time by age category
  - Average number of seizures over time by age category and by modal dose category, where modal doses will be clustered as follows: ]0;10], ]10;20], ]20;30], ]30;40].

Supportive listings will also be performed for tonic and atonic seizures, and for other types of seizures separately. The listings will include all the related data recorded in the *Subject Diary – Seizure Record* eCRF page.

### 16.2.2. Qualitative Subject Status Assessments

#### 16.2.2.1. Qualitative Subject Status Variables & Derivations

The following parameters will be used to assess the qualitative status of subjects:

- Summary and change from baseline in global impression assessments by the Investigator and parent(s)/caregiver(s)
  - Clinical Global Impression of Severity (CGI-S)
  - Clinical Global Impression of Improvement (CGI-I)
- Change from baseline in scores for:
  - Impact of Pediatric Epilepsy Scale (IPES)

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

The schedule of assessments is provided in Table 1 of the protocol. Subjects enrolled from INS011-15-054 will be excluded from IPES scores evaluation.

For CGI-S, the assessment for each subject by time point will be recorded on a scale of 1 to 7:

- 1 = Normal
- 2 = Borderline
- 3 = Mild
- 4 = Moderate
- 5 = Marked
- 6 = Severe
- 7 = Most extreme.

The CGI-I assessment for each subject will also be a scale of 1 to 7:

- 1 = Very much improved
- 2 = Much improved
- 3 = Minimally improved
- 4 = No change
- 5 = Minimally worse
- 6 = Much worse
- 7 = Very much worse.

The IPES is validated for subjects who are 2 to 16 years of age. Due to developmental delay characteristic of the study population, subjects through 18 years of chronological age will complete the IPES.

The IPES is an 11-item questionnaire in which parents rate the degree to which their child's epilepsy has affected major aspects of their family and child's health-related quality of life. This includes the impact on their child's overall health, relationships, social life, academics, self-esteem, family activities, and the parents' own hopes for their child's future. Each item is scored on a four point scale:

- 0 = Not at all (epilepsy does not affect the area in question)
- 1 = A little
- 2 = Some
- 3 = A lot (epilepsy greatly affects functioning in the given area)

All of the items are then added to produce an IPES total score. The IPES also includes a numeric scale of the child's overall quality of life ranging from 1 = "Poor" to 6 = "Excellent".

#### 16.2.2.2. Missing Data Methods for Qualitative Subject Status Variable(s)

All data will be evaluated as observed; no imputation method for missing values will be used. A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of withdrawal (for any reason). Missing data will result in a reduced sample size for that variable/parameter.

#### 16.2.2.3. Analysis of Qualitative Subject Status Variables

The qualitative subject status will be summarized as follows:

- Number of subjects (and corresponding percentage) along the 7-point scale by time point and age category separately for CGI-S and CGI-I completed by the parent(s)/caregiver(s) and the Investigator
- Shift from baseline in CGI-S score over time separately as regards if it's completed by the parent(s)/caregiver(s) or the Investigator
- Descriptive statistics (n, mean, SD, median, minimum, and maximum) over time and by age category of the actual numeric score and the change from baseline for CGI-S completed by the parent(s)/caregiver(s) and the Investigator
- Descriptive statistics (n, mean, SD, median, minimum, and maximum) over time and by age category of the actual numeric score for CGI-I completed by the parent(s)/caregiver(s) and the Investigator
- Descriptive statistics (n, mean, SD, median, minimum, and maximum) over time and by age category of actual scores and the change from baseline for the different items of IPES

For each change/shift from baseline analysis, the two baselines, as defined Section 6.2, will be used in separate tables.

Each of the above items will also be summarized by CBD status for results observed at the Follow-up visit.

Results for each assessment will be listed separately to support these tables.

# 17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

There will be no statistical comparisons between the treatment groups for safety data.

## 17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using the latest version of MedDRA central coding dictionary.

Treatment emergent adverse events (TEAEs) are defined as AEs that first occur or worsen in severity after the first administration of the study medication.

See Appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates. In the summaries, AEs will be counted only once per subject. Only those AEs that begin between start and end of study will be summarized.

Each summary described in Adverse Event section (except Section 17.1.2 and Section 17.1.3) will be repeated for TEAEs observed during the Follow-up period and presented by CBD status.

Listings will include TEAEs and Non-TEAEs.

### 17.1.1. ALL TEAES

TEAEs will be summarized by presenting the number and percentage of subjects having any TEAE, having any TEAE in each SOC, and having each individual TEAE as reported by PT. Furthermore, summaries by severity and relationship to the study medication will be presented according to the definition below. The most frequent (at least 5%) TEAEs and drug related TEAEs will also be provided.

For each summary, TEAEs will be reported by age category.

#### 17.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

#### 17.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as “unrelated”, ”unlikely”, “possible”, “probable” (increasing severity of relationship), or “unknown”. A ”related” TEAE is defined as a TEAE with a relationship to study medication as a ”possible” or ”probable” relationship to study medication. TEAEs with a missing relationship to study medication will be regarded as a “probable” relationship to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

#### 17.1.2. TEAEs Leading to Interruption of Study Medication

TEAEs leading to interruption of study medication will be identified by a response of "Dose interrupted" for the "Action taken with study medication" question on the AE page of the eCRF. For TEAEs leading to interruption of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared. Such TEAEs will also be listed separately.

#### 17.1.3. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by a response of "Dose discontinued" for the "Action taken with study medication" question on the AE page of the eCRF. For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared. Such TEAEs will also be listed separately.

#### 17.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the *Adverse Events* page of the (e)CRF. A summary of serious TEAEs by SOC and PT will be prepared. SAEs will also be listed separately.

#### 17.1.5. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the *Adverse Events* page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared. Such TEAEs will also be listed separately.

#### 17.1.6. Adverse Events of Special Interest (AESIs)

AESIs identified in Appendix 2 will be listed and summarized as follows:

- AESIs by SOC and PT
- AESIs by SOC, PT and relationship to study drug
- Related AESIs by SOC, PT and maximum severity

Two other events are of special interest and will be reported separately as follows:

- The relation between Somnolence event and the administration of Clobazam will be summarized.
- Subjects with Anemia events will be listed (values of hemoglobin, hematocrit and erythrocytes will be reported over time)

#### 17.1.7. CTC Grading for Adverse Events

No CTC grading is required for this study.

## 17.2. DEATHS

If any subjects die during the study, as recorded on the "Death Details" page of the eCRF, the information will be summarized and listed.

Primary reason for death will also be summarized by CBD status for deaths observed during the Follow-up period. CBD status will be flagged in the listing.

## 17.3. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Serum Chemistry, and Urinalysis. A list of laboratory assessments to be included in the outputs is included in Appendix 3.

Data will be provided and presented in Standard International (SI) units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline results will be summarized by time point and age category (for quantitative measurements) using descriptive statistics
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements as described in Section 17.3.1) by time point and age category
- Proportion of subjects who develop clinical laboratory result abnormalities of interest as described in Section 17.3.1

Each laboratory result will be compared, separately, to the both baselines as defined Section 6.2.

Each laboratory result measured at the Follow-up visit will also be summarized (as described above) by CBD status.

All laboratory data will be listed with abnormal values flagged.

Data from *Urine Pregnancy Test* and *Blood Draw for Plasma Level* eCRF page will also be listed.

### 17.3.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range (LLN).
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range (ULN).

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal values for liver function tests (LFTs) will also be identified and summarized by time point and age category for:

- Alanine aminotransferase (ALT) level >3 times ULN
- Aspartate aminotransferase (AST) level >3 times ULN
- Total bilirubin in excess of >2 times ULN

Markedly abnormal values for LFTs observed at the Follow-up visit will also be summarized by CBD status.

#### 17.3.2. CTC GRADING FOR LABORATORY DATA

Laboratory measurements will not be graded using the Common Toxicity grading (CTC) system.

## 17.4. ECG EVALUATIONS

Results from the central electrocardiogram (ECG) review will be included in the reporting of this study. If the first ECG is abnormal, up to an additional 2 repetitions of a specific assessment may be performed. ECG will be evaluated at Screening (for subjects who did not meet the rollover timing criteria, see Section 6.2), Day 1 and at Final Visit/Discontinuation Visit.

The following ECG parameters will be reported for this study:

- HR (Ventricular rate) (bpm)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) [QT interval corrected by Fridericia]
- RR Interval (msec)
- Rhythm
    - Sinus rhythm
    - Atrial fibrillation
    - Other
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

Handling of retests values is described Section 6.3.

The following summaries will be provided for ECG data:

- Frequency counts and shift from baseline by age category (for qualitative measurements) in separate tables
- Summary of absolute results and change from baseline by age category (for quantitative measurements) in separate tables
- Absolute value and change from baseline according to markedly abnormal criteria and age category as described in Section 17.4.1
- Listing of all data with flag for subjects meeting markedly abnormal criteria for absolute values and for change from baseline

Each ECG result will be compared to the both baselines as defined Section 6.2.

### 17.4.1. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria and summarized by time point and age category for QT interval and QTcF parameters.

- Absolute values for QT interval and QTcF will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from Baseline for QT interval and QTcF will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

## 17.5. Vital Signs

The following Vital Signs measurements will be reported at each visit:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature ($^{o}$C)

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

The following summaries will be provided for vital signs data:

- Actual and change from baseline by time point and age category
- Incidence of markedly abnormal values
- All vital signs will be listed

Each vital sign result will be compared to the both baselines as defined Section 6.2.

Each vital sign result measured at the Follow-up visit will also be summarized (as described above) by CBD status.

In addition, the subject weight will be summarized in terms of both:

- Change from baseline across each visit
- Change from baseline to Follow-up visit by CBD status

The corresponding listing will also be provided including the flag for CBD status.

### 17.5.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

| Variable | Unit | Low | High |
|---|---|---|---|
| SBP | mmHg | ≤ 90 mmHg AND<br>change from baseline ≤ -20 mmHg | ≥ 180 mmHg AND<br>change from baseline ≥ 20 mmHg |
| DBP | mmHg | ≤ 50 mmHg AND<br>change from ≤ -15 mmHg | ≥ 105 mmHg AND<br>change from baseline ≥ 15 mmHg |
| Heart rate | Bpm | ≤ 50 bpm AND<br>change from baseline ≤ -15 bpm | ≥ 120 bpm AND<br>change from baseline ≥ 15 bpm |
| Body temperature | ˚C | NA | ≥ 38.3 ˚C AND<br>change from baseline ≥ 1.1 ˚C |

Respiratory rate will be classified as Low and High according to the following age-dependent ranges (Low for values under the range and High for values above the range):

| Age Category | Normal Respiratory Rate Range (Breaths Per Minute) |
|---|---|
| < 3 years | 20-30 bpm |
| 3 -< 6 years | 20-25 bpm |

| | |
|---|---|
| 6 -< 12 years | 14-22 bpm |
| ≥ 12 years | 12-18 bpm |

## 17.6. PHYSICAL AND NEUROLOGICAL EXAMINATION

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

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

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

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

The following summary will be produced separately for physical and neurological examination:

- Number and percentage of subjects with the results (normal/ANCS/ACS) by time point and age category
- Shifts from baseline according to normal/ANCS/ACS criteria by time point and age category
- Supportive listings will also be provided

## 17.7. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) AND VINELAND ADAPTIVE BEHAVIOR SCALES (VABS)

### 17.7.1. VARIABLES & DERIVATIONS

The 2 following scales will be analyzed in term of change from baseline in scores:

- Vineland Adaptive Behavior Scales, Second Edition – Survey Interview Form including the Maladaptive Behavior Index (VABS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

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

The schedule of assessments is provided in Table 1 of the protocol. Subjects enrolled from INS011-15-054 will be excluded from VABS and C-SSRS scores evaluation.

The VABS is validated for use in subjects from birth to 90 years of age. For the first items the raw score is collected, whereas for the Maladaptive Behavior Critical Items, both frequency and severity will be recorded as follows:

Frequency:

- 0 = Never
- 1 = Sometimes
- 2 = Usually

Severity rating:

- S = Severe
- M = Moderate

The C-SSRS will evaluate the risk of suicide for patients aged >=7 years. Clinical impression will be used for patients < 7 years or for patients >=7 years with development impairment for whom the C-SSRS would be inappropriate. The appropriate C-SSRS adult version will be used in subjects 12 years of age and older.

### 17.7.2. Missing Data Methods

All data will be evaluated as observed; no imputation method for missing values will be used. A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of withdrawal (for any reason). Missing data will result in a reduced sample size for that variable/parameter.

### 17.7.3. Analysis of Variables

The qualitative subject status will be summarized as follows:

- Descriptive statistics (n, mean, SD, median, minimum, and maximum) over time and by age category of actual scores and the change from baseline for each quantitative items of VABS
- Number of subjects (and corresponding percentage) per frequency level and per severity scale for each Maladaptive Behavior Critical Items of VABS over time reported by age category
- Number of subjects (and corresponding percentage) over time and by age category per answer (Y/N) for each questions of the C-SSRS "*suicidal ideation*" item
- Number of subjects (and corresponding percentage) over time and by age category per answer (Y/N) for each questions of the C-SSRS "*suicidal behavior*" item

For change from baseline analysis, the two baselines, as defined Section 6.2, will be used in separate tables.

Each of the above items will also be summarized by CBD status for results observed at the Follow-up visit.

Results for each assessment will be listed separately to support these tables.

## 18. Data Not Summarized or Presented

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

## 19. REFERENCES

# APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

## ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If start date < study med start date, then not TEAE<br>If start date >= study med start date, then TEAE |
| | Partial | If start date < study med start date, then not TEAE<br>If start date >= study med start date, then TEAE |
| | Missing | If start date < study med start date, then not TEAE<br>If start date >= study med start date, then TEAE |
| | | |
| Partial, but known components show that it cannot be on or after study med start date | Known | Not TEAE |
| | Partial | Not TEAE |
| | Missing | Not TEAE |
| | | |
| Partial, could be on or after study med start date | Known | If stop date < study med start date, then not TEAE<br>If stop date >= study med start date, then TEAE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, then not TEAE<br>If stop date >= study med start date, then TEAE |
| | Missing | Assumed TEAE |
| | | |
| Missing | Known | If stop date < study med start date, then not TEAE<br>If stop date >= study med start date, then TEAE |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, then not TEAE<br>If stop date >= study med start date, then TEAE |
| | Missing | Assumed TEAE |

## ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If stop date < study med start date, assign as prior<br>If stop date >= study med start date and start date <= end of treatment, assign as concomitant<br>If stop date >= study med start date and start date > end of treatment, assign as post study |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, assign as prior<br>If stop date >= study med start date and start date <= end of treatment, assign as concomitant<br>If stop date >= study med start date and start date > end of treatment, assign as post treatment |
| | Missing | If stop date is missing could never be assumed a prior medication<br>If start date <= end of treatment, assign as concomitant<br>If start date > end of treatment, assign as post treatment |
| | | |
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br>If stop date < study med start date, assign as prior<br>If stop date >= study med start date and start date <= end of treatment, assign as concomitant<br>If stop date >= study med start date and start date > end of treatment, assign as post treatment |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, assign as prior<br>If stop date >= study med start date and start date <= end of treatment, assign as concomitant<br>If stop date >= study med start date and start date > end of treatment, assign as post treatment |
| | Missing | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br>If stop date is missing could never be assumed a prior medication<br>If start date <= end of treatment, assign as concomitant<br>If start date > end of treatment, assign as post treatment |
| | | |
| Missing | Known | If stop date < study med start date, assign as prior<br>If stop date >= study med start date, assign as concomitant<br>Cannot be assigned as 'post treatment' |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < study med start date, assign as prior<br>If stop date >= study med start date, assign as concomitant<br>Cannot be assigned as 'post treatment' |
| | Missing | Assign as concomitant |

# APPENDIX 2. ADVERSE EVENTS OF SPECIAL INTEREST PREFFERED TERMS

- Anemia;
- Diarrhea;
- Fatigue;
- Blood FSH decreased;
- Blood FSH increased;
- Weight decreased;
- Weight increased;
- Decreased appetite;
- Hypersomnia;
- Lethargy;
- Sedation;
- Seizure;
- Somnolence;
- Status epilepticus;
- Aggression;
- Agitation;
- Irritability;
- Acute respiratory failure;
- Dyspnea;
- Respiratory arrest.

# APPENDIX 3. LABORATORY TESTS

**Analytical Testing**

| | |
|---|---|
| Hematology | white blood cells, red blood cells, platelet count, neutrophils, lymphocytes, eosinophils, basophils, monocytes, hemoglobin, and hematocrit |
| Serum Chemistry | total protein, albumin, creatinine, Blood urine nitrogen (BUN), uric acid, total bilirubin, direct bilirubin, alkaline phosphatase, FSH, AST, ALT, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium |
| Urinalysis | specific gravity, pH, color, and presence of white blood cells (WBCs), red blood cells (RBCs), and proteins |
| Pregnancy test | β human chorionic gonadotripin (β-hCG) in urine |

# PHARMACOKINETIC STATISTICAL ANALYSIS PLAN

**Insys Development Company**

**Clinical Trial Protocol 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 or Part A of INS011-15-054**

**Pharmacokinetic Statistical Analysis Plan**
**11 July 2017**

[redacted]



Pharmacokinetic Statistical Analysis Plan
Insys Clinical Trial Protocol INS011-14-030

**SIGNATURES**

**Statistician:** [redacted] **Ph.D.**
**Title** [redacted]

**Signature/Date:** [redacted] 11 July 2017

**Pharmacokineticist:** [redacted] **Ph.D.**
**Title** [redacted]

**Signature/Date:** [redacted] 11Jul2017

**Pharmacokineticist:** [redacted] **Ph.D.**
**Title** [redacted]

**Signature/Date:** [redacted] 11Jul 2017

**Sponsor Approval:** [redacted] **Ph.D.**
**Title** [redacted]
**Insys Development Company**

**Signature/Date:** [redacted] 11JUL2017

[redacted]





## LIST OF COMMON ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ANOVA | analysis of variance |
| AUC | area under the (plasma concentration vs. time) curve |
| bid or BID | twice daily |
| BLQ | below the limit of quantitation |
| CI | confidence interval |
| CL/F | clearance after extravascular administration |
| $C_{max}$ | maximum concentration |
| CV% | percent coefficient of variation |
| h | hour(s) |
| ln | natural logarithm |
| mg | milligram(s) |
| mL | milliliter(s) |
| n or N | number of occurrences |
| N/A or NA | not applicable |
| ng | nanogram(s) |
| PK | pharmacokinetic(s) |
| qd or QD | once daily |
| SAP | statistical analysis plan |
| SD | standard deviation |
| $t_{½}$ | terminal elimination half-life |
| $T_{max}$ | time to reach $C_{max}$ |
| [redacted] | |
| Vz/F | Volume of distribution in the terminal phase after extravascular administration |
| $\lambda_z$ | apparent elimination rate constant in terminal phase |

[redacted]



Pharmacokinetic Statistical Analysis Plan
Insys Clinical Trial Protocol INS011-14-030

## STUDY TITLE

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

## STUDY OBJECTIVES

The primary objectives of this study are:

- To assess the long-term safety of Cannabidiol Oral Solution as an adjunctive treatment for subjects with treatment-resistant seizure disorders, including Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS)
- To establish the continued efficacy of Cannabidiol Oral Solution in maintaining seizure control in subjects with treatment-resistant seizures that previously completed INS011-14-029, INS011-14-024, or INS011-14-025
- To assess the global status of subjects taking Cannabidiol Oral Solution for an extended period of time determined by various qualitative assessments
- To monitor for changes in plasma levels of Cannabidiol Oral Solution during long-term treatment of subjects with treatment-resistant seizure disorders, including LGS or DS

## STUDY DESIGN

This is a multicenter, open-label study to assess the long-term safety and efficacy of Cannabidiol Oral Solution as adjunctive therapy for pediatric and adult subjects with treatment-resistant seizure disorders, including LGS and DS.

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

- Subjects who completed INS011-14-029 will initiate this study on the dose with which they were being treated previously, unless tolerability issues were observed for a particular subject. When the dose is selected for INS011-14-024 and INS011-14-025, subjects will be transitioned to that dose (a maximum of 40 mg/kg/day).
- Subjects who completed INS011-14-024 and INS011-14-025 will continue treatment with the dose at which they were being treated previously, unless tolerability issues were observed for a particular subject. This dose will be that deemed safe and tolerable in INS011-014-029.

The planned dosing regimen is twice daily administration (BID).

Dosing of the investigational product may be reduced for an individual subject as per Investigator opinion should tolerability issues arise. Treatment with established antiepileptic drugs (AEDs) will continue without interruption and changes will be permitted as necessary based on safety concerns of changes in seizure control.

Visits will be scheduled at 1 week, 2 weeks, and monthly for the first 3 months after completion of the subject's prior study, and quarterly thereafter. All subjects will complete a Final Visit/Discontinuation Visit regardless of when they stop treatment/complete the study. A Follow-up Visit will occur 2 weeks after the Final Visit/Discontinuation Visit.

At each visit, a record of the incidence and severity of AEs, treatment-emergent AEs (TEAEs), and SAEs will be collected and this will serve as a primary outcome criterion for this study. Other safety-related parameters such as 12-lead ECG and hematology, chemistry, and urinary analyses will also be assessed at each visit except the 2-week visit.

At each visit except the 1- and 2-week visits, the following qualitative assessments will be completed: Clinical Global Impression of Improvement (CGI-I), Clinical Global Impression of Severity (CGI-S), Child Behavior Checklist (CBCL) Total Problems scale, Impact of Pediatric Epilepsy Scale (IPES), Vineland Adaptive Behavior Scales (VABS), Vineland Maladaptive Behavior Scales (VMBS), and Columbia-Suicide Severity Rating Scale (C-SSRS).

Seizure diaries will be reviewed to assess control of seizures (frequency, duration, and severity) throughout the duration of the study.

Collection of Pharmacokinetic Samples

Determination of trough (pre-dose) plasma levels of cannabidiol (CBD) and its 7-OH metabolite (7-OH-CBD) will be performed. Samples for assessment of CBD and 7-OH CBD trough plasma levels will be collected immediately prior to administration of the morning dose of the investigational product at the following times:

- Visit 2 (Day 1, Week 0)
- Visit 5 (Week 4)
- Visit 6 (Week 8)
- Visit 7 (Week 12)
- Visit 8 (Week 24)
- Visit 9 (Week 36)
- Visit 10 (Week 48, TBD; final visit)*
- Visit 11 (Week 50, TBD; 2 weeks after final visit)*

*Subjects continuing on study medication as part of the Expanded Access Program will be flagged in the concentration-time listings; the concentration-time data for this subset of the population will summarized in a secondary set of tables and figures.

[redacted]



For patients taking clobazam, plasma levels of clobazam and its major metabolite norclobazam will also be measured.

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

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

## PHARMACOKINETIC METHODS

Concentration-time data will be analyzed using Phoenix™ WinNonlin® (Version 6.3 or higher, Pharsight Corporation) or other appropriate software. These data will support safety monitoring and establish the extent of variability during long-term treatment with the investigational product.

### Pharmacokinetic Population

The PK population consists of patients who receive at least one dose of CBD and have at least one usable CBD plasma concentration measurement.

### Concentration-Time Data Tabulation

Concentration data of CBD, 7-OH-CBD, clobazam, and norclobazam (N-desmethylclobazam), if applicable, will be presented in a data listing. The listing will include Subject ID, Subject Alias, Visit (or Week), Actual Time Post Dose (if available), CBD Dose, Clobazam Dose, formulation, and dosing frequency (if applicable), and concentration (units) for each analyte.

Concentration data of CBD and 7-OH-CBD will be tabulated and summarized by CBD dose level (based on the daily dosing regimen, mg/kg/day, of CBD when the plasma sample is taken) at each collection time (scheduled week) using descriptive statistics (n, mean, SD, minimum, median, maximum, and percent coefficient of variation). In addition, dose-normalized concentrations of CBD and 7-OH-CBD will be tabulated and summarized by clobazam flag

(yes/no) at each collection time (scheduled week) using descriptive statistics. CBD and 7-OH-CBD concentration-time data for subjects continuing on study medication as part of the Expanded Access Program will summarized in a secondary set of tables and figures.

Concentration data of clobazam and norclobazam will be stratified by clobazam flag (yes/no), tabulated, and summarized using descriptive statistics.

In the data tabulation and summarization, concentrations below the lower limit of quantitation (BLQ) will be set to zero.

Plots of mean concentration-time for CBD and 7-OH-CBD and dose-normalized CBD and 7-OH-CBD will be created by CBD dose level, with and without stratification by clobazam (yes/no). Plots of concentration-time data for CBD and 7-OH-CBD for individual subjects will be created; since the dose level may vary during the study, the dose level at a given sample time will be labeled or foot-noted (if possible) in the figure. Plots for clobazam and norclobazam will be stratified by subjects on clobazam therapy (yes/no).

Pharmacokinetic Calculations

The metabolite-to-parent ratio (MRCtrough) will be calculated using concentrations of 7-OH CBD (metabolite) and CBD (parent) at each Visit, starting with the first trough sample obtained and through the remaining visits. If either CBD or 7-OH CBD concentration is not reportable or BLQ, MRCtrough will be reported as "not applicable". MRCtrough for clobazam will be calculated using the same methodology.

To assess the degree of accumulation during long-term BID administration of cannabidiol oral solution after 1 month treatment (Visit 5), an accumulation ratio (RCtrough) will be estimated using the dose-normalized trough plasma concentrations of CBD and 7-OH-CBD at each Visit, according to:

$$RCtrough = Conc/D(n^{th} \text{ visit dose})/Conc/D(5^{th} \text{ visit dose}),$$

where $Conc/D(n^{th}$ visit dose) is the dose-normalized trough concentration at a given Visit beyond 1 month (i.e, $n^{th}$) and $Conc/D(5^{th}$ visit dose) is the dose-normalized trough concentration determined at Visit 5 (scheduled on Week 4). If either $Conc/D(n^{th}$ visit dose) or Conc/D(5th visit dose) is not reportable or BLQ, RCtrough will be reported as "not applicable".

RCtrough and MRCtrough will be tabulated and summarized by CBD dose level (based on the daily dosing regimen, mg/kg/day, of CBD when the plasma sample is taken) at each collection time (week) using descriptive statistics (n, mean, SD, minimum, median, maximum, and percent coefficient of variation). MRCtrough for clobazam will be stratified by clobazam flag (yes/no), tabulated, and summarized using descriptive statistics.

[redacted]



## REPORTING

The pharmacokinetic tables and figures described in this PK SAP will be presented in the listings section of the clinical study report (CSR) for INS011-14-030. Appropriate numbering to be provided by the medical writer.

## GENERAL REFERENCES


- "Guidance For Industry: Statistical Approaches to Establishing Bioequivalence" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) January 2001.
- "Guidance For Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) March 2003.
- "Guidance For Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) December 2002.
- "Guidance For Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) February 2012.
- Brian P. Smith, Francois R. Vandenhende, Karl A. DeSante, Nagy A. Farid, Pamela A. Welch, John T. Callaghan, and S. Thomas Forgue, "Confidence Interval Criteria for Assessment of Dose Proportionality", Pharmaceutical Research, Vol. 17, No. 10, 2000; p.1278-1283.

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Pharmacokinetic Statistical Analysis Plan
Insys Clinical Trial Protocol INS011-14-030

## EXAMPLE TABLES AND FIGURES

Concentration listing with descriptive statistics

| | | | | Visit | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 2 | 5 | 6 | 7 | 8 | 9 | 10 |
| **Analyte** | **CBD_Dose (mg/kg)** | **Subject_ID** | **Subject_Alias** | **Concentration (ng/mL)** | | | | | | |
| Cannabidiol | 5.00 | xxx | xxx | | | | | | | |
| | | | n | | | | | | | |
| | | | Mean | | | | | | | |
| | | | SD | | | | | | | |
| | | | Min | | | | | | | |
| | | | Median | | | | | | | |
| | | | Max | | | | | | | |
| | | | CV% | | | | | | | |

*Similar format for each analyte, dose level, and for dose-normalized concentrations*

Concentration summary table

| | | Visit 2 | | | Visit 5 |
|---|---|---|---|---|---|
| **Analyte** | | **Concentration (ng/mL)** | **DN_Concentration (ng/mL/mg/kg)** | **CBD_Dose (mg/kg)** | |
| Cannabidiol | n | | | | |
| | Mean | | | | |
| | SD | | | | |
| | Min | | | | |
| | Median | | | | |
| | Max | | | | |
| | CV% | | | | |
| | Geometric Mean | | | | |

*Similar table for 7-OH CBD*

[redacted]



Pharmacokinetic Statistical Analysis Plan
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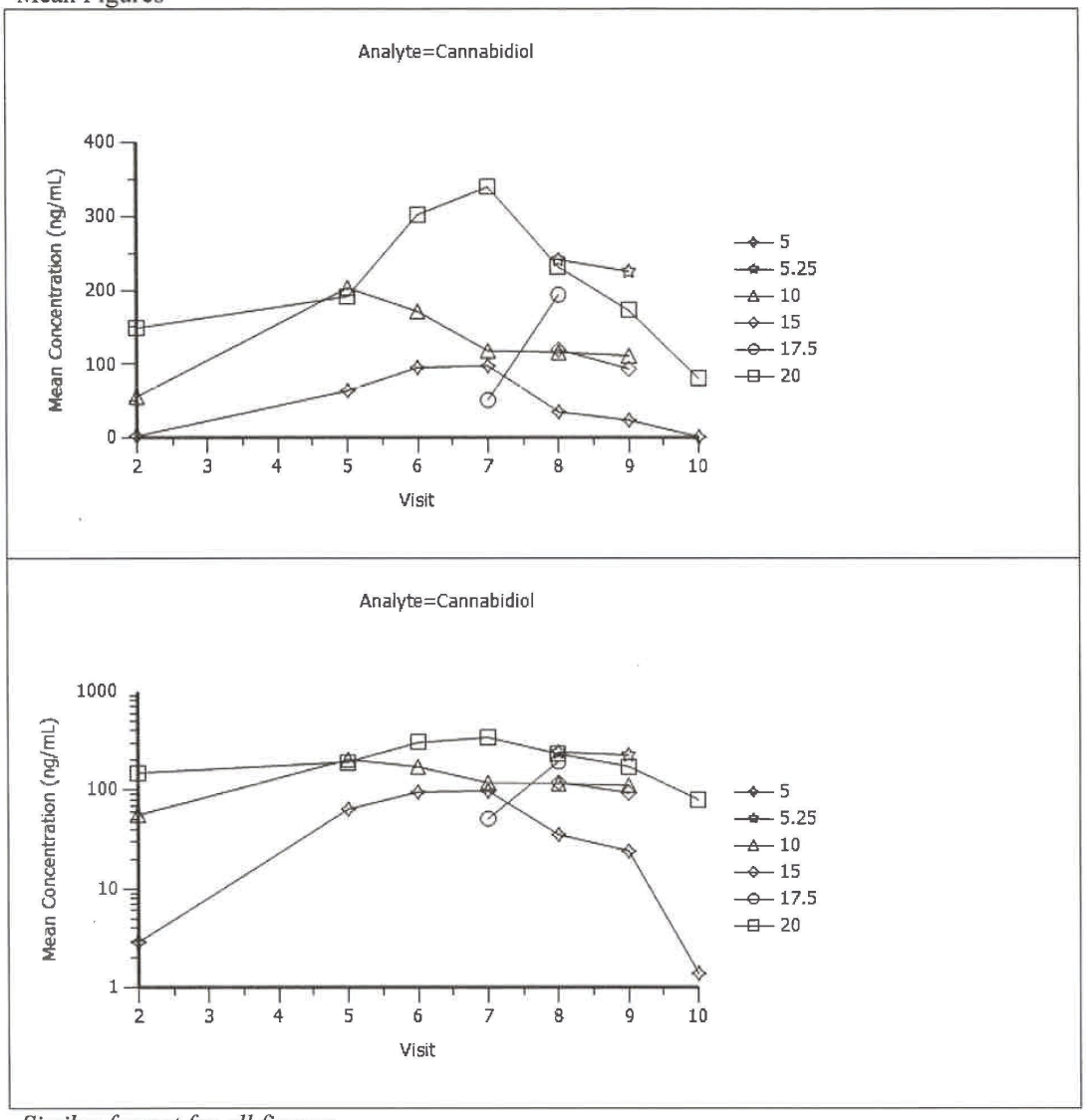
Mean Figures




*Similar format for all figures*

[redacted]



Pharmacokinetic Statistical Analysis Plan
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MRCtrough table

| | | | Visit | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 2 | 5 | 6 | 7 | 8 | 9 | 10 |
| **CBD_Dose (mg/kg)** | **Subject_ID** | **Subject_Alias** | **MRCTrough_CBD** | | | | | | |
| 5.00 | xxx | xxx | | | | | | | |
| | | n<br>Mean<br>SD<br>Min<br>Median<br>Max<br>CV% | | | | | | | |

RCtrough table

| | | | | Visit | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 6 | 7 | 8 | 9 | 10 |
| **Analyte** | **CBD_Dose (mg/kg)** | **Subject_ID** | **Subject_Alias** | **RCTrough** | | | | |
| Cannabidiol | 5.00 | xxx | xxx | | | | | |
| | | | n<br>Mean<br>SD<br>Min<br>Median<br>Max<br>CV% | | | | | |

[redacted]





Concentration listing

| Analyte | Subject ID | Subject Alias | Visit | Week | CBD Daily Dose (mg/kg/day) | Prior Visit CBD Dose (mg/kg) | Clobazam Dose (mg) | Route Of Clobazam | Dose Frequency Of Clobazam | Conc (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|---|
| CBD | xxx | xxx | 5 | 4 | 20.00 | 10.00 | 10.00 | ORAL | QD | xxx |
| CBD | xxx | xxx | 6 | 8 | 20.00 | 10.00 | 10.00 | ORAL | QD | xxx |
| CBD | xxx | xxx | 7 | 12 | 20.00 | 10.00 | 10.00 | ORAL | QD | xxx |

Note: This listing will be based on the analysis data set provided by the statistician or biostatistics group.