Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy, Safety, and Tolerability of Cannabidiol Oral Solution for the Treatment of Patients with Prader-Willi Syndrome

Protocol Number: INS011-16-085
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Insys Development Company, Inc.

Protocol No.: INS011-16-085

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Efficacy, Safety and Tolerability of Cannabidiol Oral Solution for the Treatment of Patients with Prader-Willi Syndrome

Covance Study ID: 000000163564

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Covance Inc. CDCS

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Sponsor Name: Insys Development Company, Inc.
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Clinical Development Commercialization Services

Table of Contents

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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

PPD

Signature 09 Jul 2018 Date

PPD / Principal Statistician

Printed Name/Title

Insys Approval:

PPD

Signature PPD 10 Jul 2018 Date

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Statistical Analysis Plan

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-16-085 Covance Study ID: 000000163564

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PPD / Senior Clinical Trial Manager

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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	Internal draft 1.0	Covance
	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	9 July 2018	

Glossary of Abbreviations

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CBD	Cannabidiol
CI	Confidence Interval
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CTMS	Clinical Trials Management System
DEXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
HQ-CT	Hyperphagia Questionnaire for Clinical Trials
IMP	Investigational medicinal product
ITT	Intent-to-treat
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LS	Least squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects model for repeated measures
MNAR	Missing not at random
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity

PK	Pharmacokinetic
PP	Per-protocol
PROMIS®	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
PWS	Prader-Willi syndrome
QTcF	Fridericia corrected QT interval
SAP	Statistical analysis plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TFEQ-R18	Three Factor Eating Questionnaire – 18-item version
TFLs	Tables, Figures and Listings
THC	Tetrahydrocannabinol

1. Source Documents

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

Document	Date	Version
Protocol Amendment 1	18 May 2018	3.0
eCRF	31 May 2018	1.0

2. Protocol Details

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the efficacy of Cannabidiol Oral Solution on hyperphagia-related behavior in patients with Prader-Willi Syndrome (PWS) as measured by the total score of the Hyperphagia Questionnaire for Clinical Trials (HQ-CT).

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the efficacy of Cannabidiol Oral Solution on the change in total body weight in patients with PWS.
- To assess the responder rate (responder is defined as a 6-point decrease on the HQ-CT from Baseline to End of Study).
- To assess the efficacy of Cannabidiol Oral Solution by measuring Patient Global Impression of Change (PGI-C).
- To assess the safety and tolerability of Cannabidiol Oral Solution in patients with PWS.
- To assess the efficacy of Cannabidiol Oral Solution on eating behavior in patients with PWS as measured by the Three Factor Eating Questionnaire -18-item version (TFEQ-R18).
- To assess the impact on Quality of Life in patients with PWS as measured by the PROMIS® Life Satisfaction and Positive Affect short-form questionnaires.
- To assess the impact on physical activity in patients with PWS as measured by the PROMIS® Physical Activity and Fatigue questionnaires.

2.1.3 Exploratory Objective

The exploratory objective of this study is to assess the efficacy of Cannabidiol Oral Solution on body composition and bone mineral density, as measured by dual-energy X-ray absorptiometry (DEXA).

2.2 Overall Study Design

This study is a double-blind, randomized, placebo-controlled, Phase 2 clinical trial in patients aged 8 to 17 years inclusive, with a genetically confirmed diagnosis of PWS.

Approximately 66 patients will be randomized in a 1:1 ratio to receive either:

- Cannabidiol Oral Solution (40 mg/kg/day) divided into twice daily doses with standard meal
- Matching placebo, divided into twice daily doses with standard meal

Randomization will be stratified according to use of growth hormone (Yes, No).

Patients will participate in the study for approximately 19 weeks. The study will consist of the following 6 periods:

- Screening Period (2 weeks)
- Placebo Lead-in Period (2 weeks)
- Titration Period (1 week)
- Maintenance Period (12 weeks)
- Taper Period (1 week)
- Follow-up Period (1 week)

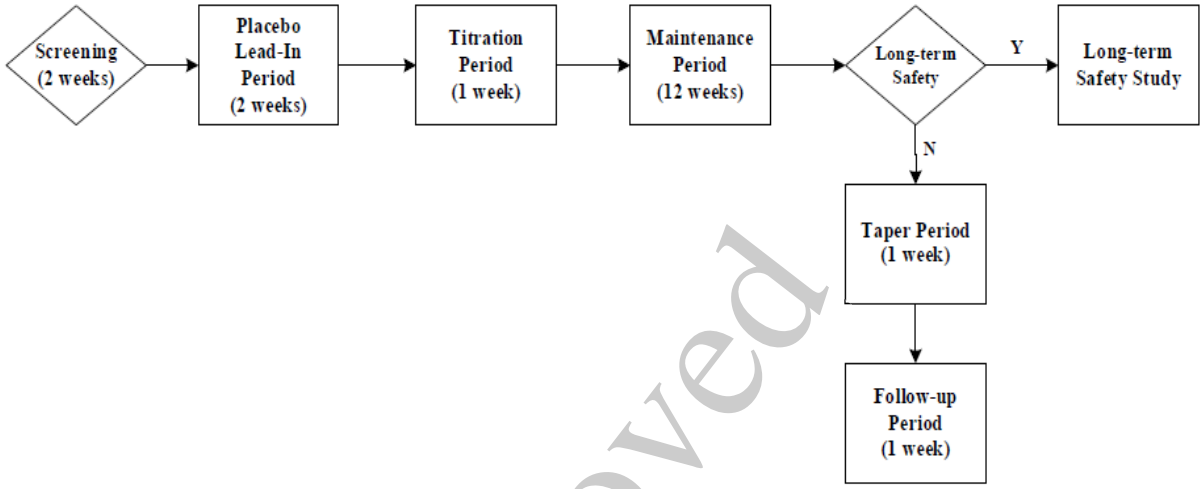
Eligible patients will be assigned to a 2-week single-blind placebo lead-in period after which they will be randomly assigned to receive double-blind treatment with either Cannabidiol Oral Solution (40 mg/kg/day) or matching placebo (a 1-week Titration Period followed by a 12-week Maintenance Period). During the Titration Period Cannabidiol Oral Solution will be titrated as follows: Days 1-3: 20 mg/kg/day, Days 4-6: 30 mg/kg/day, Day 7: 40 mg/kg/day.

During the Maintenance Period, patients may have their dose of blinded study medication adjusted down to 30 mg/kg/day at the discretion of the investigator or qualified designee based on the patient's tolerability.

After completion of the study, patients will be offered an opportunity to enroll into an open-label, long-term safety study. Patients who do not elect to enroll in the long-term safety study will be titrated off study drug over 7 days and a final safety follow-up phone call will be placed 2 weeks after study completion for patients who do not elect to continue in the long-term safety study.

The study design is depicted in Figure 1.

Figure 1: Study Design Schematic



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

2.3 Sample Size and Power

A total of 30 patients per treatment group will provide at least 85% power with an alpha of 0.05, to detect a difference in the change in HQ-CT from Baseline to Week 13 of 5 points with a standard deviation of 6. Assuming a 20% drop out rate, approximately 66 patients (33 patients per arm) will be randomized to achieve 60 (30 patients per arm) completers.

3. Efficacy and Safety Endpoints

3.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint for this study is change in the total score of the HQ-CT from Baseline (defined as the score after the Placebo lead-in period) through Study Completion (Week 13/Early Withdrawal). 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 then obtained by summing the responses to each item, yielding a total HQ-CT score that can range from 0 to 36 (Fehnel, et al., 2015).

3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- Change in total body-weight from Baseline through Study Completion/Early Withdrawal.
- Responder rate (responder is defined as 6-point decrease on the HQ-CT from Baseline through Study Completion).
- Patient Global Impression of Change and Severity.
- Change in the TFEQ-R18 from Baseline through Study Completion/Early Withdrawal. The TFEQ-R18 yields scores for 3 subscales: cognitive restraint, uncontrolled eating and emotional eating (Karlsson et al., 2000). The scores for each subscale will be analyzed separately.
- Change in Quality of Life (PROMIS® Life Satisfaction and Positive Affect questionnaires) from Baseline through Study Completion/Early Withdrawal.
- Change in physical activity (PROMIS® Physical Activity and Fatigue questionnaires) from Baseline through Study Completion/Early Withdrawal.

Methods for scoring the TFEQ-R18 and the PROMIS® questionnaires are provided in Appendix B and Appendix C respectively.

3.3 Exploratory Efficacy Endpoint

The exploratory efficacy endpoint is change in body composition from Baseline to Study Completion/Early Withdrawal as measured by DEXA.

3.4 Safety Endpoints

The safety endpoints of this study are:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory assessments
- Vital signs (blood pressure, pulse rate, respiration rate and temperature)
- 12-lead ECGs
- Physical examination assessments
- Pregnancy screens
- Urine drug screen (including THC)
- Medical history
- Prior and concomitant medications.

4. Pharmacokinetic Endpoints

The pharmacokinetic (PK) endpoints of this study are trough concentrations (C_{trough}) of cannabidiol (CBD) and metabolite 7-OH-CBD which will be used to assess the exposure-response relationship.

5. Analysis Populations

Unless otherwise stated, all efficacy analyses will be performed on the Intent-to-treat (ITT) population. A supportive analysis of the primary endpoint will also be performed on the Per-protocol (PP) population. All safety analyses will be performed on the safety population. Analyses of the DEXA endpoints will be performed on the DEXA population. The analysis of the PK endpoints will be performed on the PK population.

5.1 Intent-to-treat Population

The ITT population will consist of all randomized patients. ITT patients are analyzed according to their randomized treatment.

5.2 Safety Population

The Safety population includes all randomized patients treated with at least one dose of the study drug during the double-blind treatment period. Safety patients are analyzed according to their actual treatment received.

5.3 Per Protocol Population

The PP population will consist of all patients in the ITT population who do not have any important protocol deviations leading to exclusion from the PP population.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Section 5.3.1 details the deviations.

All important and non-important protocol deviations are defined in a protocol deviations list which includes details about escalation requirements and whether they are detected via monitoring or programming.

5.3.1 Important Protocol Deviations Leading to Exclusion from the PP Population Analysis

Only the important protocol deviations considered as having a major effect on the collection or interpretation of the efficacy data will lead to complete exclusion of patients from the PP population.

For the purposes of this study, the following criteria have been identified as important protocol deviations leading to exclusion from the PP population as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint:

Table 1: Important Protocol Deviations Leading to Exclusion from the PP Population

Type	Important Protocol Deviation Leading to Exclusion from the PP Population	Method of Identification
Non-compliance during the double-blind treatment phase	Patients who had low study drug compliance (e.g. repeated occurrence of compliance < 90%)	**Programmable** check based on the exposure and drug accountability data.
Errors in treatment allocation	Patients who receive the wrong treatment at 1 or more study visit due to packaging or dispensing errors	**Programmatic** check based on the unblinded IWRS database after the study is unblinded. The check will be performed by comparing the kit number assigned by IWRS to the patient at a particular visit against the kit number actually used.
CTMS	Covance Clinical will provide the list of protocol deviations based on the clinical monitoring.	**Manual** review: The list will be reviewed and the important protocol deviations that will lead to exclusion from the PP population will be identified.

As defined in Table 1, the majority of the important protocol deviations leading to exclusion from the PP population will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock.

All important protocol deviations leading to exclusion from the PP population occurring during the study will be reviewed and approved by Insys prior to database lock and unblinding. Should additional important protocol deviations leading to exclusion from the PP population, not anticipated at the time of preparing this SAP, be identified during the study (and prior to unblinding) they will be documented in a SAP amendment and included in all relevant protocol deviation reviews and approvals.

5.4 DEXA Population

The DEXA population is a pre-defined subpopulation of approximately 20 patients from the ITT population for whom changes in body composition (total fat, lean body mass and bone mineral content) are assessed via DEXA scans.

5.5 PK Population

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

6. DATA Handling

6.1 Time points and Visit Windows

Day 1 is defined as the date of first dose of double blind treatment. 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.

For all populations, 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.

6.2 Handling of Dropouts, Missing Data, and Outliers

Missing data will not be imputed for the safety analyses. Safety 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.

6.2.1 Observed Cases Analysis

A mixed effects model for repeated measurements (MMRM) will be used to analyze the primary and continuous secondary efficacy endpoints. This model is based on the assumption that the missing data follow a missing at random (MAR) mechanism and uses only observed data. There are no imputations of missing data for this analysis.

6.2.2 Jump to Reference

A reference-based multiple imputation approach, jump to reference, may be used as a sensitivity analysis of the primary efficacy endpoint. This analysis is based on the assumption that the missing data follow a missing not at random (MNAR) mechanism. For this analysis, it is assumed that the distribution of values at future visits for patients in the CBD treatment group who discontinue early is similar to that of patients with observed data in the control arm.

No rules for outlier detection are planned.

7. Statistical Methods

7.1 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 for main effects and 10% significance level for interaction terms
Treatment group labels and order presented	Listings: Placebo Cannabidiol Oral Solution (30 mg/kg/day) Cannabidiol Oral Solution (40 mg/kg/day) Tables: Placebo CBD (30 mg/kg/day) CBD (40 mg/kg/day) All CBD Total
Tables	Data in summary tables presented by treatment group and visit (where applicable)
Listings	All data collected presented by Treatment group Patient Visit (where applicable) Date; unless otherwise specified
Descriptive summary statistics for continuous variables	Number of patients/observations (n) Mean Standard deviation (SD) Median Minimum Maximum

Principle	Value
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 Mean Difference Median Percentages
Display to two more decimal places than collected value	Standard Deviation Confidence Interval
Limit of precision for displays	3 decimal places
Date Format	DDMMMYYYY

Baseline is defined as the last scheduled or unscheduled measurement collected prior to first dose of double-blind investigational medicinal product (IMP) treatment.

Only data from scheduled post-baseline visits will be included in analyses and summary tables, all visit data will be listed.

7.2 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:

- screened;
- entered placebo lead-in period;
- screened and not randomized;
- randomized (i.e. entered the titration period);
- randomized and not treated with double-blind treatment;
- treated with double-blind treatment;
- entered the maintenance period;
- entered the taper period;

- continued to the long-term safety study;
- included in each study population (Safety, ITT, PP, DEXA, PK).

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 randomization by site will also be provided by treatment group and overall for the ITT population. Inclusion/exclusion criteria not met will be listed for all screened patients.

In addition, a summary table and listing will be produced for discrepancies between the stratification factors in the database and IWRS. This will be produced for the ITT population.

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

7.3 Protocol Deviations

All important protocol deviations leading to exclusion from the PP population (see Section 5.3.1) will be summarized by treatment group for the ITT population. The deviations will be identified before data are unblinded.

All protocol deviations will be listed.

7.4 Demographics and Other Baseline Characteristics

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

- age (years) [calculated as (screening visit date – date of birth)/365.25 and reported as whole 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 Screening visit;
- body mass index (kg/m^2) (derived on eCRF);
- randomization strata of growth hormone treatment (Yes, No).

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.

7.4.1 Patient Global Impression of Severity (PGI-S)

Patient Global Impression of Severity (PGI-S) is assessed at Baseline and is a single item questionnaire where patients are asked to rate the severity of their condition. The response to this assessment ranges from 1: "Normal" to 7: "Extremely ill (I am more sick/ill than I have ever been". PGI-S response will be summarized by treatment group using standard descriptive statistics. In addition, the number and percentage of patients selecting each response will be summarized.

7.4.2 Medical or Surgical History

Medical or surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 21.0 (or a later version if updated during the study)]. All medical or surgical history will be listed, and the number and percentage of patients with any medical or surgical history will be summarized for the ITT population by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

7.4.3 Previous and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by Covance using the WHODrug 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 taken prior to the first dose date of double-blind IMP treatment.

Concomitant medications are those with a start date on or after the first dose date of double-blind IMP treatment, or those with a start date before the first dose date of double-blind IMP treatment and a stop date on or after the first dose date of double blind treatment or ongoing at the end of the 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 the ITT 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.

7.5 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 Safety 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 Safety population.

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

7.6 Efficacy

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

7.6.1 Primary Efficacy Analysis

The primary endpoint, change in total HQ-CT score from Baseline through Study Completion/Early Withdrawal, will be assessed using MMRM.

The MMRM model will include change in total HQ-CT score at each scheduled visit, fixed factors for treatment group, time (study week), randomization strata of growth hormone treatment (yes, no), a treatment-by-time interaction term, and baseline total HQ-CT as a covariate. A contrast will be specified for the primary analysis time point of Study Completion/Early Withdrawal.

All patients in the ITT population with non-missing total baseline HQ-CT score and at least one non-missing post-baseline HQ-CT score will be included in the analysis model. The MMRM will use observed data only, no imputations of missing data will be performed. Stratification factors as used in the IWRS randomization will be

included. An unstructured covariance matrix will be used to model the residuals over time within each patient. However, in the event that the model does not converge, the following matrices will be used in order until the model converges: Toeplitz, first-order autoregressive and compound symmetry. The least squares (LS) means and their associated 95% confidence intervals (CIs) and p-values will be presented for each treatment group, as well as the LS mean difference, its 95% CI and the comparison p-value.

Graphical presentations of total HQ-CT scores by treatment and visit will be used to examine trends over time, displaying the LS means together with their associated 95% CIs.

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

This analysis will be repeated for all patients in the per protocol population.

7.6.2 Sensitivity Analysis

The MMRM is based on the assumption that missing data follow a MAR mechanism. A sensitivity analysis, based on the assumption that the missing data are MNAR, may be performed for the primary endpoint. The implementation of this analysis will depend on the extent and pattern of missing data and as such, it may not be used. For this sensitivity analysis, missing values will be imputed using jump to reference where it is assumed that following early discontinuation, the values for patients in the CBD group at future visits will follow the same distribution as the values of patients in the placebo group.

Each of the complete datasets will be analyzed using an Analysis of Covariance (ANCOVA) model which will model the change in total HQ-CT score from Baseline to Study Completion/Early Withdrawal and which will include fixed factors for treatment group and randomization strata of growth hormone treatment (yes, no), and baseline HQ-CT total score as a covariate. The results from the analyses of each complete dataset will then be combined using Rubin's method.

LS means and the LS mean difference between all CBD and placebo will be presented together with the relevant 95% CIs and p-values.

7.6.3 Multiplicity

Statistical inference for the primary endpoint and for the secondary endpoints [change in total body weight, responder rate, PGI-C, TFEQ-R18 (3 subscales), PROMIS® Life Satisfaction and Positive Affect (2 separate scores) and PROMIS® Physical Activity and Fatigue (2 separate scores)] will be controlled at an overall family wise error rate of α =0.05 using a gatekeeping approach. Using this

approach, the hypotheses associated with the secondary endpoints will only be tested if the null hypothesis for the primary endpoint is rejected (i.e. if $p<0.05$ for the primary endpoint).

In this instance, the 10 hypotheses corresponding to the secondary endpoints will be tested using the Hochberg procedure. The 10 p-values resulting from the inferential analyses of the secondary endpoints will be ordered from largest to smallest and will be compared with alpha critical values of $\alpha, \alpha/2, \alpha/3, \ldots \alpha/(10-1)$. The largest p-value is then compared with α. If this p-value is not less than α, proceed to the second largest p-value and compared it with $\alpha/2$. Testing continues sequentially in this manner until a p-value for an endpoint is statistically significant. Once a p-value is statistically significant, conclude that the treatment effect for that endpoint and all endpoints with smaller p-values are statistically significant.

7.6.4 Secondary Efficacy Analysis

The analyses of the secondary efficacy endpoints will be based on the placebo and all CBD treatment groups in the ITT population. Descriptive statistics for the secondary efficacy endpoints will be based on all treatment groups, i.e. placebo, CBD (30 mg/kg/day), CBD (40 mg/kg/day), all CBD and total.

Listings of secondary efficacy endpoint data will be produced for the ITT population.

7.6.4.1 Change in Total Body Weight

Change from Baseline to Study Completion/Early Withdrawal in body weight will be analyzed using the MMRM method described for the primary efficacy endpoint. The MMRM model will include change in total body weight at each scheduled visit, fixed factors for treatment group, time (study week), randomization strata of growth hormone treatment (yes, no), a treatment-by-time interaction term, and baseline total body weight as a covariate.

LS means and the LS mean difference between all CBD and placebo will be presented together with the relevant 95% CIs and p-values. In addition, LS means and the 95% CIs will be plotted by treatment group and visit.

7.6.4.2 Responder Rate

A responder is defined as a 6-point decrease in HQ-CT total score from Baseline to Study Completion/Early Withdrawal. The responder rate data will be analyzed using Fisher's exact test and patients with missing HQ-CT score at Study Completion/Early Withdrawal will be treated as non-responders.

The proportion of responders and non-responders will be presented by treatment group, together with the difference in proportion, its associated 95% CI and the

comparison p-value from the Fishers exact test. The proportion of responders will be plotted by treatment group and visit.

7.6.4.3 PGI-C

PGI-C will be analyzed using the MMRM method described for the primary efficacy endpoint, which will include PGI-C at each scheduled visit, fixed factors for treatment group, time (study week), randomization strata of growth hormone treatment (yes, no), a treatment-by-time interaction term, and PGI-S score at baseline as a covariate.

LS means, the LS mean difference between all CBD and placebo, as well as the relevant 95% CIs and p-values will be presented. A plot of the LS means and their associated 95% CIs by treatment group and visit will be produced.

7.6.4.4 Change TFEQ-R18

Change from Baseline to Study Completion/Early Withdrawal in each TFEQ-R18 subscale will be analyzed using the MMRM method described for the primary efficacy endpoint. For each subscale, the MMRM model will include change in TFEQ-R18 subscale score at each scheduled visit, fixed factors for treatment group, time (study week), randomization strata of growth hormone treatment (yes, no), a treatment-by-time interaction term, and baseline TFEQ-R18 subscale score as a covariate.

LS means and the LS mean difference between all CBD and placebo will be presented together with the relevant 95% CIs and p-values. In addition, LS means and the 95% CIs will be plotted by treatment group and visit.

7.6.4.5 Change in Quality of Life

Quality of life will be assessed using the PROMIS® Life Satisfaction and Positive Affect short-form questionnaires. Change in PROMIS® Life Satisfaction from Baseline to Study Completion/Early Withdrawal and change in PROMIS® Positive Affect from Baseline to Study Completion/Early Withdrawal will be analyzed separately using the MMRM described for the analysis of the primary endpoint.

The MMRM analysis described for the primary endpoint will be used to analyze the change in PROMIS® score (Life Satisfaction or Positive Affect) from Baseline to Study Completion/Early Withdrawal. For each analysis, change in PROMIS® score (Life Satisfaction or Positive Affect) at each visit will be included in the model, together with fixed factors for treatment group, time (study week), randomization strata of growth hormone treatment (yes, no), a treatment-by-time interaction

term, and baseline PROMIS® score (Life Satisfaction or Positive Affect) as a covariate.

The resulting LS means, LS mean difference between all CBD and placebo, 95% CIs and corresponding p-values will be presented. LS means and the 95% CIs will be plotted by treatment group and visit.

7.6.4.6 Change in Physical Activity

Physical Activity will be assessed using the PROMIS® Physical Activity and Fatigue questionnaires. Change in PROMIS® Physical Activity from Baseline to Study Completion/Early Withdrawal and change in PROMIS® Fatigue from Baseline to Study Completion/Early Withdrawal will be analyzed separately using the MMRM described for the analysis of the primary endpoint.

For each analysis, change in PROMIS® score (Physical Activity or Fatigue) from Baseline to Study Completion/Early Withdrawal, the MMRM model will include change in PROMIS® score (Physical Activity or Fatigue) at each scheduled visit, fixed factors for treatment group, time (study week), randomization strata of growth hormone treatment (yes, no), a treatment-by-time interaction term, and baseline PROMIS® score (Physical Activity or Fatigue) as a covariate.

LS means and the LS mean difference between all CBD and placebo will be presented together with the relevant 95% CIs and the comparison p-value. In addition, LS means and the 95% CIs will be plotted by treatment group and visit.

7.6.5 Subgroup Analysis

Not applicable.

7.6.6 Exploratory Efficacy Analysis

The exploratory efficacy analysis will be based on the DEXA population. Total fat, fat free mass, bone mineral content and lean body mass, together with changes from baseline will be summarized by treatment group and visit using standard descriptive statistics.

All DEXA scan data will be listed.

7.6.7 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 ITT population.

7.7 Safety

7.7.1 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 Safety population.

7.7.2 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [Version 21.0 (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 double-blind IMP and up to 14 days after the last dose of double blind IMP or events with start date prior to the date of first dose of double-blind IMP whose severity worsens on or after the date of first dose of double-blind IMP.

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.

Summary tables of TEAEs by treatment group and overall will be produced for the Safety 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 the Safety population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- AEs occurring in the run-in period, by SOC and PT;
- 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.

7.7.3 Laboratory Evaluations

7.7.3.1 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 Safety 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.

7.7.3.2 Urine Drug Screen

A urine sample for the following assessments will be collected at the Screening visit: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine and tetrahydrocannabinol.

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

7.7.3.3 Urine Pregnancy Test

A urine dipstick pregnancy test will be performed on all female patients at the Screening visit.

Pregnancy screen results will be listed for the Safety population

7.7.4 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);
- respiratory rate (breaths/min);
- body temperature (°C);
- 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 Safety population.

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

7.7.5 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 Safety 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 Safety population. Shifts from baseline at each post-baseline visit will be presented.

A listing of ECG measurements and findings will be produced for the Safety population.

7.7.6 Physical Examination

Physical examination results (normal/abnormal) and details of abnormalities will be listed for the Safety population.

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 Safety Population.

7.8 PK Analysis

One pre-dose sample at Baseline, Week 5, Week 9 and Study Completion/Early Withdrawal will be drawn for the determination of the plasma levels of CBD and 7-OH-CBD. The analysis of the PK data has been described in a separate PK SAP.

All PK data will be listed.

7.9 Interim Analysis

No interim analysis will be performed for this study.

8. Changes in Planned Analysis

Not applicable.

9. Data Issues

Not applicable.

Statistical Analysis Plan

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-16-085 Covance Study ID: 000000163564

10. References

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Varni, J. W., Magnus, B., Stucky, B. D., Liu, Y., Quinn, H., Thissen, D., et al. (2014). Psychometric properties of the PROMIS® pediatric scales: precision, stability and comparison of different scoring and administration options. *Quality of Life Research, 23*(4), 1233-1243.

Statistical Analysis Plan

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-16-085 Covance Study ID: 000000163564

Appendix A: Visit Schedule Chart

Assessment	SCREENING (2 Weeks)	SINGLE BLIND PLACEBO LEAD-IN (2 Weeks)	DOUBLE-BLIND TREATMENT PHASE									FOLLOW-UP PERIOD[b] (2 Week)
			TITRATION PERIOD[a] (1 Week)			MAINTENANCE PERIOD (12 Weeks)						
Visit Number	1	2	3 Baseline	Call/ Email	4	5	6	7	8	9	10 Study Completion / Early Withdrawal	11
Study Time Point	Week -4 to -2	Week -2	Day 1	Day 3 & 6	Day 7	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Week 15
Visit Window (Days)	±3	±3	±3	0	0	±3	±3	±3	±3	±3	±3	±3
Informed consent/assent (if appropriate)	X											
Medical/surgical history	X											
Demographics	X											
Review of inclusion and exclusion criteria	X											
Randomization			X									
Physical exam	X	X	X		X	X	X	X	X	X	X	
Record vital signs	X	X	X		X	X	X	X	X	X	X	
Resting 12-lead ECG	X						X		X		X	
Clinical laboratory tests[d]	X					X					X	
Urinalysis	X										X	

Statistical Analysis Plan

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-16-085 Covance Study ID: 000000163564

Assessment	SCREENING (2 Weeks)	SINGLE BLIND PLACEBO LEAD-IN (2 Weeks)	DOUBLE-BLIND TREATMENT PHASE									FOLLOW-UP PERIOD[b] (2 Week)
			TITRATION PERIOD[a] (1 Week)			MAINTENANCE PERIOD (12 Weeks)						
Visit Number	1	2	3 Baseline	Call/ Email	4	5	6	7	8	9	10 Study Completion / Early Withdrawal	11
Study Time Point	Week -4 to -2	Week -2	Day 1	Day 3 & 6	Day 7	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Week 15
Visit Window (Days)	±3	±3	±3	0	0	±3	±3	±3	±3	±3	±3	±3
Urine dipstick for females of childbearing potential only	X										X	
Urine drug screen (drugs of abuse including THC)	X											
Dosing with Study Medication		X	X	X	X	X	X	X	X	X	X	
Dispense/Review/Collect study medication		X	X	X	X	X	X	X	X	X	X	X
Hyperphagia Questionnaire for Clinical Trial (HQ-CT)	X	X	X		X	X	X	X	X	X	X	
Weight	X	X	X		X	X	X	X	X	X	X	
Three Factor Eating Questionnaire (TFEQ-R18)			X			X			X		X	
PROMIS Life Satisfaction and Positive Affect pediatric short-form questionnaires			X			X			X		X	

Statistical Analysis Plan

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-16-085 Covance Study ID: 000000163564

Assessment	SCREENING (2 Weeks)	SINGLE BLIND PLACEBO LEAD-IN (2 Weeks)	DOUBLE-BLIND TREATMENT PHASE									FOLLOW-UP PERIOD[b] (2 Week)
			TITRATION PERIOD[a] (1 Week)			MAINTENANCE PERIOD (12 Weeks)						
Visit Number	1	2	3 Baseline	Call/ Email	4	5	6	7	8	9	10 Study Completion / Early Withdrawal	11
Study Time Point	Week -4 to -2	Week -2	Day 1	Day 3 & 6	Day 7	Week 3	Week 5	Week 7	Week 9	Week 11	Week 13	Week 15
Visit Window (Days)	±3	±3	±3	0	0	±3	±3	±3	±3	±3	±3	±3
PROMIS Physical Activity and Fatigue pediatric short-form questionnaires			X			X			X		X	
Patient Global Impression of Severity (PGI-S)			X									
Patient Global Impression of Change (PGI-C)						X			X		X	
DEXA scan[e]			X								X	
Columbia Suicide Severity Rating Scale (C-SSRS)			X								X	
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Review of adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics[c]			X				X		X		X	

DEXA = Dual energy X-ray absorptiometry; PROMIS = Patient-Reported Outcomes Measurement Information System

[a] Titration schedule = Days 1-3: 20 mg/kg/day; Days 4-6: 30 mg/kg/day; Day 7: 40 mg/kg/day. Phone calls will be made at Day 3 and Day 6 to determine if the patient's dose may be titrated to the next dose level.

Statistical Analysis Plan

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-16-085 Covance Study ID: 000000163564

[b] The Follow-up Visit is only for patients who do not choose to enroll in the long-term safety study and are tapering off the study drug. Patients will return to the site for assessment of concomitant medications, AEs, and to return and reconcile study drug.
[c] Blood draws for trough pharmacokinetic analyses of CBD and metabolite 7-OH-CBD will be collected prior to morning dose at Visit 3 (Baseline) and Visit 6, 8, and 10 during the Maintenance Period.
[d] Blood and urine samples for hematology, chemistry, and urinalysis will be collected at Screening (visit1), and Study Completion (Visit 10)/Early Withdrawal. Blood sample for complete blood count (CBC) will be collected at Week 3 (Visit 5).
[e] DEXA scan will be completed on a subset of 20 patients.

Appendix B: Scoring of the TFEQ-R18

The TFEQ-R18 assessment is comprised of 3 subscales:

- Cognitive restraint: items 2, 11, 12, 15, 16 and 18
- Uncontrolled eating: items 1, 4, 5, 7, 8, 9, 13, 14 and 17
- Emotional eating: items 3, 6 and 10

The TFEQ-R18 responses are scored following the method described by de Lauzon, et al. (2004). Responses to items 1-17 are given a score between 1 and 4. For item 18, scores ranging from 1-2 are coded as 1, scores ranging from 3-4 are coded 2, scores ranging from 5-6 are coded 3 and scores ranging from 7-8 are coded 4.

The score for each subscale is obtained by summing the scores for each of the items included in that subscale. The raw scores are then transformed so that the resulting scores range from 0 - 100. The transformation is performed using the following formula:

$$\frac{\text{raw score - lowest possible raw score}}{\text{possible score range}} \times 100$$

In instances where patients do not answer all of the questions, scores for each subscale will be imputed provided the patient answered at least half of the items for that particular subscale. The imputed score for that subscale is obtained by calculating the mean score for the items the patient responded to within that subscale and imputing that mean score for the items in that subscale with missing responses.

Higher scores for each of the 3 subscales correspond to greater cognitive restraint, greater uncontrolled eating and greater emotional eating.

Appendix C: Scoring of the PROMIS® Questionnaires

The PROMIS® pediatric assessments are scored to yield standardized T-scores which have a mean of 50 and a standard deviation of 10 relative to the general population. For example, if a patient has a T-score of 60 for fatigue, they are reporting fatigue that is one standard deviation higher than that of the general population average.

Details on the validation of the assessments can be found in Varni, et al. (2014) and Stone, et al. (2016).

The PROMIS® instruments offer a scoring service, the HealthMeasures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice), which accommodates missing data in instances when patients fail to respond to all of the items for a particular instrument. The PROMIS® instruments are scored using item-level calibrations and the scoring service uses the responses to each item for each participant, as well as item response theory, to generate a standardized T-score for each participant. Item response theory is a family of mathematical models which assigns unique values to each item based on how likely people with different levels of a particular measured trait are to endorse that item.

Responses to each of the PROMIS® instruments (life satisfaction, positive affect, physical activity and fatigue) will be read into the HealthMeasures Scoring Service tool in a .csv file where the first column is the patient ID (PIN), the second column is the assessment number (Assmnt, e.g. 1 for first assessment and 2 for second assessment) and the remaining columns correspond to the unique question numbers for that particular instrument.

The scoring service then produces a spreadsheet with the T-scores that will be used for the analyses of the PROMIS® outcomes.

Statistical Analysis Plan

Sponsor Name: Insys Development Company, Inc.
Sponsor Protocol ID: INS011-16-085 Covance Study ID: 000000163564

The formats for the .csv files for each instrument are given below.

Life Satisfaction (PROMIS Ped SF v1.0 – Life Satisfaction 8a):

PIN	Assmnt	SWB_LS_046R1	SWB_LS_048R1	SWB_LS_051R1	SWB_LS_019R1	SWB_LS_004R1	SWB_LS_003R1	SWB_LS_006R1	SWB_LS_055R1
xxxxxx	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x

Positive Affect (PROMIS Ped SF v1.0 – Positive Affect 8a):

PIN	Assmnt	SWB_P_027R1	SWB_P_025R1	SWB_P_026R1	SWB_P_029R1	SWB_P_037R1	SWB_P_049R1	SWB_P_001R1	SWB_P_004R1
xxxxxx	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x

Physical Activity (PROMIS Ped SF v1.0 – Physical Activity 8a):

PIN	Assmnt	PAC_M_009R1	PAC_M_105R1	PAC_M_002R1	PAC_M_008R1	PAC_M_010R1	PAC_M_011R1	PAC_M_114R1	PAC_M_134R1
xxxxxx	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x

Fatigue (PROMIS Ped SF v2.0 – Fatigue 10a):

PIN	Assmnt	4239aR2r	4212R1r	4213R1r	2876R1r	4221R1r	4220R1r	4210R2r	4241R2r	4208bR2r	4196R1r
xxxxxx	x	x	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x	x	x
xxxxxx	x	x	x	x	x	x	x	x	x	x	x