Statistical Analysis Plan (SAP)

Sponsor Name:	Sunovion Pharmaceuticals Inc.
Protocol Number and Title:	SEP360-310 An Open-label, Flexibly-dosed, 26-Week Extension Safety Study of Dasotraline in Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD)
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I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Full Form
ADHD	attention deficit hyperactivity disorder
ADHD RS-IV HV	ADHD Rating Scale Version IV – Home Version (modified for investigator administration)
AE	Adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
ß-hCG	beta-human chorionic gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
CGI-S	Clinical Global Impression - Severity
Conners 3-P	Conners 3rd Edition - Parent
CSR	Clinical study report
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia – Suicide Severity Rating Scale
DB baseline	double-blind baseline
DB treatment	double-blind treatment (i.e. treatment received during SEP360-202)
DBL	database lock
DESS	Discontinuation-Emergent Signs and Symptoms (DESS) Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ET	early termination

Abbreviation	Full Form
HR	heart rate
ICH	International Conference on Harmonization
ITT	intent-to-treat
KM	Kaplan-Meier
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
n/a	not applicable
OL baseline	open-label baseline
PR	time between P wave and QRS in electrocardiograph
PT	preferred term
PWC	Physician Withdrawal Checklist (PWC)
QRS	electrocardiographic wave (complex or interval)
QT	electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
SAE	serious adverse experience/event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
WBC	white blood cells
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WFIRS-P	Weiss Functional Impairment Rating Scale – Parent Report

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the efficacy and safety analyses defined by appropriate data listings, summary tables, and figures, as well as statistical methodologies, are outlined in this document and provide valid conclusions about the study objectives.

2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings.

The analyses of efficacy, safety for the clinical study report (CSR) are planned to be completed after the database lock (DBL).

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

To evaluate the long-term safety and tolerability of flexibly-dosed dasotraline in children and adolescents with ADHD by the incidence of adverse events (AEs; or serious AEs [SAEs]), and AEs (or SAEs) leading to discontinuation.

3.2. SECONDARY OBJECTIVE(S)

The secondary objectives are:

- To evaluate the long-term safety and tolerability of flexibly-dosed dasotraline in children and adolescents with ADHD by assessing clinical laboratory evaluations, vital signs, physical examinations, body height and weight, 12-lead electrocardiograms (ECG), Tanner Staging, Children's Sleep Habits Questionnaire (CSHQ), and the frequency and severity of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS) Children's Assessment.

- To assess the long-term effectiveness of dasotraline in children and adolescents with ADHD using the following assessments:

    - the ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV)

- the Clinical Global Impression – Severity (CGI-S)
- the Conners 3rd Edition Parent (Conners 3-P)

- To evaluate health-related quality of life and functional impairment in children and adolescents with ADHD using the Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P).
- To assess potential withdrawal symptoms following discontinuation of dasotraline treatment using the following assessments (administered during the withdrawal period):
  - Discontinuation-Emergent Signs and Symptoms (DESS) Scale
  - Physician Withdrawal Checklist (PWC)

4. STUDY DESIGN

4.1. BRIEF DESCRIPTION

This is an open-label, flexibly-dosed, 26-week extension study in children and adolescents with ADHD who have completed 6 weeks of double-blind treatment in the core study (SEP360-202). Subjects who meet all eligibility criteria will transition directly from the core study and will not need to complete the End of Study (EOS) visit in the core study. Subjects will take the first dose of open-label study drug in this extension study on Day 1, the morning following the open-label (OL) Baseline visit. Subjects will continue to take study drug for 26 weeks, at approximately the same time each morning including on the days when clinic visits occur. Dasotraline will be dosed at 2 mg/day for the first week of the study (Days 1 - 7). Subjects will then be flexibly dosed (2, 4, or 6 mg/day) thereafter beginning on Day 8 based on the investigator's assessment of effectiveness and tolerability. After the OL Baseline visit, subjects will return to the clinic weekly for the first 2 weeks, once every 2 weeks for the next 4 weeks, then once every 4 weeks for the remainder of the treatment period for clinical evaluation, and once at the end of the withdrawal period (Visit 13E). At the approximate midpoint between the scheduled monthly visits (i.e., 14 ± 2 days after a visit) during the treatment period, the site staff will contact the subject's parent/legal guardian via telephone, text, or email in order to evaluate the safety of the subjects as well as to remind subject/parent/legal guardian about adherence to study drug administration and upcoming visits, following which, if necessary, an unscheduled visit can be arranged.

All assessments will be performed as per the schedule of assessment in Appendix 1.

4.2. DETERMINATION OF SAMPLE SIZE

This study is projected to enroll up to 330 subjects based on the number of subjects who complete the core study.

5. STUDY ENDPOINTS

5.1. PRIMARY ENDPOINT

The primary endpoint is:

- The incidence of overall AEs (or SAEs), and AEs (or SAEs) leading to discontinuation.

5.2. SECONDARY ENDPOINTS

The secondary endpoints are:

- Clinical laboratory evaluations (serum chemistry, hematology, lipid panel, thyroid function panel, urinalysis, sex hormones).
- Clinical evaluations (vital signs, physical examination, body height and weight, Tanner Staging, and 12-lead ECG).
- Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS.
- Change in CGI-S score.
- Change in ADHD-RS-IV HV total score.
- Change in the inattentiveness and hyperactivity subscales of the ADHD-RS-IV HV.
- Change in Conners 3-P total score and subscale scores (Oppositional, Cognitive problems, Hyperactivity, and ADHD Index).

- Change in CSHQ total score and 8 subscale scores (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness).

- Change in WFIRS-P total score and 6 domain scores (family, school learning behavior, life skills, child's self-concept, social activities, and risky activities).

- Symptoms of withdrawal using:

    - PWC score

    - DESS score

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

- All analyses and summaries will be produced using SAS® version 9.3 (or higher) for windows.

- All statistical summaries will be presented based on the treatment received in the double-blind core study (SEP360-202), called DB treatment. Because the treatment received in SEP360-310 is flexible, the treatment groups for summary in SEP360-310 will be labeled as:

    - placebo / dasotraline flexible,

    - dasotraline 2 mg/day / dasotraline flexible,

    - dasotraline 4 mg/day / dasotraline flexible,

    - dasotraline combined / dasotraline flexible, and

    - total.

- The dasotraline combined group will include those subjects who were treated in SEP360-202 with dasotraline 2 mg/day and dasotraline 4 mg/day.

- Summaries will also be presented by visits (Double-Blind Baseline, Open-Label Baseline, Weeks 1, 2, 4, 6, 10, 14, 18, 22, 26, Week 26 or Treatment Period LOCF,

and EOS). See the details for the DESS and PWC for discussion of the display of visits for those summaries.

- Unless otherwise specified, continuous variables will be summarized with descriptive statistics including: n, arithmetic mean, standard deviation (SD), 95% confidence interval for the mean, median, minimum, and maximum values. All categorical/qualitative data will be presented using frequency counts and percentages. Shift tables will be produced for some assessments and will contain counts and percentages of subjects in each cross-classification level of baseline versus post-baseline assessment. Only subjects with a non-missing value for both baseline and post-baseline, at a given visit, will be included in these tables.

- The listings will be provided using the enrolled population (defined in Section 8.1). For listings related to analyses conducted using the intent-to-treat population, a flag will be shown in the subject column identifying subjects who were excluded from the intent-to-treat population. In general, the subject listings will be sorted by the treatment group, subject number and assessment date (and time, if applicable).

- Data for unscheduled assessments will be included when selecting worst result for shift analyses, and for summary of normal/abnormal values. The summary of observed value and change from DB baseline and change from OL baseline data will be performed by nominal visits (scheduled visits). Unscheduled assessments will be included in Week 26 or Treatment Period LOCF, as long as that unscheduled assessment was not completed more than 3 days after the last dose of study medication.

6.2. KEY DEFINITIONS

6.2.1. Baseline Value

Two different baseline values are defined for this study.

The first baseline value, called the DB baseline, is the baseline value from the double-blind core study, SEP360-202. This value is the last non-missing assessment value up to and including the day of first dose of study drug in SEP360-202.

The second baseline value, called the OL baseline, is defined as Week 6 (LOCF) from the core study, SEP360-202, which is also the assessment at the start of SEP-360-310. For

the questionnaire based endpoints, domain scores for the Week 6 (LOCF) may come from different assessment dates. This occurs when an incomplete questionnaire was completed at the Week 6 assessment of SEP360-202.

For assessments completed at the EOS assessment, a third baseline value is defined as the last assessment on treatment. This baseline will be the SEP360-310 LOCF value.

6.2.2. Study Day

Study day is defined as the number of days from the date of first dose in the SEP360-310 study to the event/visit date. It is calculated as follows:

If event date falls on or after the date of first dose then

Study Day = Event or Visit Date – First Dose Date + 1

If event date falls before the date of first dose then

Study Day = Event or Visit Date – First Dose Date

Hence, the date of first dose is referred to as Day 1. The previous day is Day -1.

6.2.3. Missing Data and Last Observation Carried Forward (LOCF)

Methods for handling missing item responses on the questionnaire instruments (i.e. ADHD-RS-IV HV, Conners 3-P, and WFIRS-P) are described in different sections later on.

If a subject discontinues the study prematurely, the last available data (excluding early termination visit assessments if done more than 3 days after the last dose of study medication, unscheduled assessments after the early termination assessment if done more than 3 days after the last dose of study medication, and Withdrawal Period assessments) will be carried forward to the study endpoint (i.e. the LOCF approach) at Week 26. Visits earlier than the early termination date for subjects who discontinued the study prematurely will be included in the LOCF process, even if they are more than 3 days after the last dose of study medication.

The AE and concomitant medication start/end dates will be imputed based on the rules described in Appendix 3.

6.2.4. Visit Windows

All data will be organized and analyzed according to the scheduled times as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF) except for early termination (ET) visits during the treatment period.

If a subject terminates early and within the 26-week treatment period, the ET visit will be remapped based on the study day of the visit as follows.

ET Day Criteria	Visit
1 ≤ study day ≤ 10	Week 1
11 ≤ study day ≤ 17	Week 2
18 ≤ study day ≤ 31	Week 4
32 ≤ study day ≤ 45	Week 6
46 ≤ study day ≤ 73	Week 10
74 ≤ study day ≤ 101	Week 14
102 ≤ study day ≤ 129	Week 18
130 ≤ study day ≤ 157	Week 22
158 ≤ study day, but not more than 3 days after treatment termination	Week 26

If a subject already has a scheduled visit at the mapped visit time, then the ET visit will be assigned as unscheduled at that mapped study week. If more than 1 observation is collected at a scheduled visit after baseline, the earliest value (based on collection or visit date) will be used at the visit, and other value(s) will be set as unscheduled. If the early termination visit date is more than 3 days after the date of last dose, then the visit will be assigned as unscheduled if EOS is available, or the visit will be assigned as EOS if EOS is missing.

These ET visit remapping rules will apply to all data points. All tables and figures will be presented by the remapped visit. All data listings will be reported using the visit as denoted on the eCRF.

6.2.5. Pooling of Centers

There will be no statistical analyses of endpoints by pooled centers in this study.

7. SUBJECT DISPOSITION

Subject disposition will be summarized for the enrolled population. Subjects who took at least one dose of study medication will be summarized by DB treatment and overall.

Subjects who completed the study and discontinued early from the study will be summarized by DB treatment and overall. The summary of subject disposition by discontinuation reason will be presented. If there are multiple reasons for discontinuation, the primary reason (determined by the investigator) will be used for the summary. All percentages will be based on the number of enrolled subjects within each DB treatment group and overall.

Using the safety population (defined in Section 8.2), the number of days until treatment discontinuation will be analyzed using Kaplan-Meier (KM) methodology. Subjects who complete the study treatment period will be censored on the study day of the last dose. Median, 25th percentile, and 75th percentile for days until discontinuation will be presented for each DB treatment and overall. A Kaplan-Meier plot will be used to display these results.

A listing of study completion will be provided for all enrolled subjects, with flags provided to identify subjects in the safety and ITT populations.

8. ANALYSIS POPULATIONS

8.1. ENROLLED POPULATION

The Enrolled population includes all subjects with an informed consent. All disposition summaries will be performed in the enrolled population.

8.2. SAFETY POPULATION

The Safety population includes all subjects who enter this study and receive at least one dose of study drug. All safety analyses will be performed in the Safety population.

8.3. INTENT-TO-TREAT (ITT) POPULATION

The ITT population is defined as all subjects who enter this study and receive at least one dose of study drug, and have a baseline effectiveness measure and at least one post baseline effectiveness measure in ADHD-RS-IV HV. The ITT population will be used for the effectiveness and quality of life analyses.

For the definition of ITT, the baseline effectiveness measure for determination of inclusion in the population is the OL baseline value.

9. PROTOCOL DEVIATIONS

Protocol deviations will be collected during monitoring visits. These deviations will be placed into the following categories: concomitant medications, dosing, enrolment criteria, laboratory, non-compliance, visit schedule, visit/procedure requirement, and other.

A summary table will be provided as the number and percentage of subjects with at least one important protocol deviation and the number of subjects in each category. A listing will be provided containing all protocol deviations.

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

10.1. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics (collected at enrollment into the SEP360-202 study) (sex, race, ethnicity, age [years], age group [6-9 and 10-12 years], weight [kg], height [cm], body mass index [BMI, kg/m^2], and World Health Organization (WHO) z-scores and percentiles for height and BMI) will be summarized by DB treatment and overall for the safety and ITT populations. These values will be referred to as DB baseline values.

The age, age group [6-9 and 10-13 years], weight, height, BMI, and WHO percentiles for height and BMI at the time of enrollment into the SEP360-310 study will be summarized by DB treatment and overall for the safety and ITT populations. These values will be referred to as OL baseline values. Note that some subjects who were 12 years old at entry into SEP360-202 had turned 13 years old at the time of entry into SEP360-310.

Sex, race, age group, and ethnicity will be summarized by using summary statistics for categorical variables (frequencies and percentages). Percentages for sex, race, age group, and ethnicity will be based on the number of subjects within a DB treatment group. The DB baseline and OL baseline values for Age, height, height percentile, weight, BMI, and BMI percentile will be summarized by using summary statistics for continuous variables (number of subjects, arithmetic mean, standard deviation, 95% confidence interval for mean, median, minimum and maximum values).

Age will be calculated as the number of years between date of birth and date of enrollment into the SEP360-202 and SEP360-310 studies.

BMI (kg/m^2) = Weight(kg)/(Height(m))^2

Normal age and sex-based percentiles for weight, height, and BMI will be determined using the WHO growth charts.

BMI category: Underweight (< 5 percentile), Normal (≥ 5 - < 85 percentile), Overweight (≥ 85 - < 95 percentile), Obese (≥ 95 percentile).

A listing of demographic data will be provided for the enrolled population.

10.2. HISTORY

10.2.1. Medical History

In SEP360-202, medical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0). For subjects who enrolled in SEP360-310, the medical history data collected during the SEP360-202 study will be carried over into the SEP360-310 study database. The count and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT), will be summarized by DB treatment and overall. Percentages will be based on number of safety subjects within DB treatment group. Additionally, if a subject had 1 or more history events under any given SOC or PT, the subject will be counted only once under that SOC or PT.

A listing of medical history will be provided for the enrolled population.

10.2.2. Psychiatric History

Psychiatric history will be summarized by DSM-5. The psychiatric history data collected during the SEP360-202 study will be carried over into the SEP360-310 study database. The count and percentage of subjects under each DSM-5 code will be summarized by DB treatment and overall. All percentages will be based on the number of safety subjects within a DB treatment group. If a subject had 1 or more history events more than once, the subject will be counted only once under any given DSM-5 code.

A listing of psychiatric history will be provided for the enrolled population.

10.3. PRIOR AND CONCOMITANT MEDICATIONS

All medications will be coded using the World Health Organization drug dictionary (WHODRUG) version Quarter 1 2016 (March 1st, 2016). Medications ongoing at the time of completion of the SEP360-202 study will be carried over into the SEP360-310 study database.

The prior medications will include medications started prior to the first dose date of open-label study drug. The concomitant medications will include medications used on or after the first dose date of open-label study drug. Concomitant medications will include prior medications that continued use on or after the first dose of open-label study drug.

Concomitant medications will be separated into the following subsets:

- Medications used during the treatment period excluding medications that started on or after the **last** dose of open-label study drug
- Medications with start date on or after the first dose date of open-label study drug; this subset may include medications that had a change in dosage or frequency of use that had been used prior to open-label treatment.
- Medications started on or after the last dose of open-label study drug

For the summary tables, the count and percentage of subjects under each anatomical therapeutic chemical (ATC) class level 2 and PT will be summarized by DB treatment and overall. If a subject has taken 1 or more prior or concomitant medications more than once, the subject will be counted only once under any given drug class.

A listing of prior and concomitant medications will be provided for the enrolled population. Flags will be included in the listing to distinguish prior versus concomitant medications and to identify medications started on or after the last dose of open-label study drug.

10.4. TREATMENT EXPOSURE AND COMPLIANCE

Each subject will be dispensed one to three 10-day blister card(s) per scheduled visit based on his or her next expected visit date. Subjects will take 1 capsule of study medication per day at approximately the same time each morning. The number of capsules dispensed, the number of capsules returned, along with corresponding dates will be captured on the CRF and used to calculate exposure and compliance to study medication in terms of the number of doses taken.

First dose date in the SEP360-310 study will be based on the date of intake on the Dosing Accountability record. If the date of intake is missing on this record, it will be assumed the subject initiated one day after the first dispensation of SEP360-310 medication.

The last dose date will be based on the investigator's provided date on the disposition page. If the last dose date on the disposition page is missing, then last dose date will be based on the last date of intake from the Dosing Accountability log form that corresponds to the last dispensation of study drug.

Duration of Exposure (days) = Last dose date – first dose date + 1.

If a subject has only the first dose date and missing last dose date, the duration of exposure will be counted as 1 day.

If the subject has drug dispensed, but the first dose date is missing and the last dose date is missing, the duration of exposure will be counted as 1 day.

The duration of exposure to SEP360-310 study drug (number and percentage of subjects with exposure to study drug ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥= 70 days, ≥ 84 days, ≥ 98 days, ≥ 112 days, ≥ 154 days, ≥ 168 days, ≥ 182 days) will be summarized by DB treatment and overall.

Cumulative exposure to dasotraline across the SEP360-202 and SEP360-310 studies will be summarized by DB treatment and overall. Cumulative exposure to dasotraline for a subject who received double-blind Placebo in the SEP360-202 study will be limited to the duration of treatment in the SEP360-310 study. Duration of treatment will be categorized as (≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days , ≥ 28 days, ≥ 42 days, ≥ 56 days, ≥ 70 days, ≥ 84 days, ≥ 98 days, ≥ 112 days, ≥ 126 days, ≥ 140 days, ≥ 154 days, ≥ 168 days, ≥ 182 days, ≥ 196 days, ≥ 210 days, and ≥ 224 days).

Duration of SEP360-310 dose will also be provided by DB treatment group and overall. The number of days each dose was taken will be summarized.

The summary will also include the average daily dose (mg) for all subjects, the average daily dose (mg) for subjects who complete the study, the modal daily dose (mg) for all subjects, and the modal daily dose (mg) for subjects who complete the study. The modal daily dose will also be reported for each visit. The average daily dose is calculated as [(2*number of days 2 mg was taken) + (4*number of days 4 mg was taken) + (6*number of days 6 mg was taken)] / (date of last dose – date of first dose + 1). For each subject the modal daily dose is defined as the dose taken most frequently. Unscheduled visits will also be considered in the calculations when reporting data at each visit. If 2 or more different doses were taken an equal number of days, then modal

dose will equal the dose that the subject last takes. The number of days each dose was used will be summarized. Also, the total person-years during SEP360-310 will be summarized. The total person-years is defined as the sum of the duration of dosing in days for all subjects divided by 365.25.

A bar chart will summarize the percentage of subjects taking 2 mg, 4 mg, and 6 mg at each visit.

A summary will also be provided for the changes in dose from the previous visit. Categories that will be summarized include: maintained dose at 2 mg, down-titrated to 2 mg, up-titrated to 4 mg, maintained dose at 4 mg, down-titrated to 4 mg, up-titrated to 6 mg, maintained dose at 6 mg. Data from unscheduled visits will also be considered when assigning categories. The category will represent the change from the most recent visit. If the dose was changed during an unscheduled visit, then the category will represent the change from the most recent unscheduled visit.

Treatment compliance will be determined for each subject at each visit and over all visits. A descriptive summary will be provided.

Compliance = (Capsules Dispensed – Capsules Returned)*100/Capsules Expected. Subjects are expected to take 1 capsule per day. Only visits with both capsules dispensed and capsules returned will be included. For overall compliance if the number of capsules returned is missing for one or more visits for a subject, then overall compliance will be considered missing for that subject.

Subjects who take less than 75% of scheduled doses or who take more than 125% of scheduled doses will be considered noncompliant.

11. EFFECTIVENESS ANALYSIS

11.1. CHANGE IN ADHD-RS-IV

The first effectiveness endpoint is the change from DB baseline and change from OL baseline in Attention Deficit Hyperactivity Disorder Rating Scale-fourth edition (ADHD RS-IV) HV total score. The primary study population is the ITT population.

The ADHD RS-IV HV includes 18 questions about frequency of recent symptoms of ADHD. ADHD RS-IV HV score is collected at each visit. Each question is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms) with total score ranging from 0 to 54. The 9 odd-numbered items (i.e. 1, 3, 5, 7, 9, 11, 13, 15, and 17) assess inattentive symptoms, and the 9 even-numbered items (i.e. 2, 4, 6, 8, 10, 12, 14, 16, and 18) assess hyperactive-impulsive symptoms. Hence, for inattention subscale, the score is obtained by adding the responses to the scores of the 9 odd-numbered items, and for the hyperactivity-impulsivity subscale, the score is obtained by adding the scores of the 9 even-numbered items. The total score is obtained by adding the inattention and hyperactivity-impulsivity subscale scores.

The observed value, change from DB baseline, and change from OL baseline for the ADHD RS-IV total score will be summarized descriptively by DB treatment and overall, and by visit (Week 1, Week 2, Week 4, Week 6, Week 10, Week 14, Week 18, Week 22, Week 26, and Week 26 (LOCF)).

The line-plot of Mean (±SE) change from DB baseline in ADHD RS-IV HV total score will be provided by DB treatment and overall, and visit using the ITT population. At baseline, the change from baseline will be displayed as 0. A similar line-plot will be produced showing the change from OL baseline.

11.1.1. Percentage of responders at Post-Baseline Visits

A subject is defined as a responder if they have a ≥ 30% (and ≥ 50%) improvement in ADHD RS-IV HV total score compared with the DB baseline.

A similar definition for responder will be defined if the subject has a >= 30% (and >= 50%) improvement in ADHD RS-IV HV total score compared with the OL baseline.

The number of subjects with such responses compared to DB baseline and OL baseline will be summarized by DB treatment and overall, and by visit for the ITT population.

11.2. CHANGE IN CGI-S

The CGI-S modified assessment asks the clinician one question: “Considering your total clinical experience with this population, how mentally ill is the subject at this time?” The clinician’s answer is rated on the following 7-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects.

The analysis will be performed using the same methodology described above for the ADHD RS-IV endpoint, using the ITT population.

The line-plot of Mean (±SE) change from DB baseline and OL baseline in CGI-S score will be provided by DB treatment and overall, and by visit.

11.3. CHANGE FROM BASELINE IN THE ADHD RS-IV HV INATTENTIVENESS AND HYPERACTIVITY SCORES

For the hyperactivity-impulsivity and inattentiveness subscales of the ADHD RS-IV HV, the same methodology used for the ADHD RS-IV HV Total score described in section 11.1 will be used.

11.4. CHANGE FROM BASELINE IN CONNERS 3-P SCALE SCORES

The Conners 3rd Edition - Parent (Conners 3–P) assesses behaviors and other concerns in children between the ages of 6 and 18, inclusive. The full-length version of the Conners 3–P will be used. Assessments of Conners 3-P are completed at each clinic assessment visit as well as assessment of the child's behavior over the past week prior to the parent's assessment. The full-length version provides a thorough assessment of ADHD and addresses comorbid disorders such as Oppositional defiant disorder (ODD) and conduct disorder. Responses to the Conners 3-P will be used to calculate the scale scores.

The item numbers associated with each scale are noted below.

Conners 3-P Content Scales

Inattention (10 items)

12. Has trouble staying focused on one thing at a time.
23. Has a short attention span.
28. Avoids or dislikes things that take a lot of effort and are not fun.
44. Has trouble concentrating.
47. Doesn't pay attention to details; makes careless mistakes.
49. Has trouble changing from one activity to another.
67. Inattentive, easily distracted.
77. Gets bored.
88. Gives up easily on difficult tasks.
95. Has trouble keeping his/her mind on work or play for long.

Hyperactivity/Impulsivity (14 items)

19. Fidgeting.
43. Blurts out answers before the question has been completed.
45. Is constantly moving.
50. Excitable, impulsive.
52. Gets over-stimulated.
54. Acts as if driven by a motor.
55. Blurts out the first thing that comes to mind.
61. Has difficulty waiting for his/her turn.
69. Runs or climbs when he/she is not supposed to.
71. Is noisy and loud when playing or using free time.
93. Leaves seat when he/she should stay seated.
98. Fidgets or squirms in seat.
99. Restless or overactive.
104. Interrupts others (for example, butts into conversations or games).

Learning Problems (9 items)

5. Spelling is poor.
7. Does not understand what he/she reads.
9. Is good at memorizing facts. (R)
15. Forgets things already learned.
36. Has trouble with reading.
51. Needs extra explanation of instructions.
53. Learns information as separate facts; does not “get the big picture.”
60. Reads slowly and with a lot of effort.
87. Cannot grasp arithmetic.

Executive Functioning (9 items)

34. Fails to finish things he/she starts.
37. Has trouble getting started on tasks or projects.
63. Completes projects at the last minute.
72. Is good at planning ahead. (R)
75. Forgets to turn in completed work.
79. Fails to complete schoolwork, chores, or tasks (even when he/she understands and is trying to cooperate).
84. Has trouble organizing tasks or activities.
90. Is messy or disorganized.
97. Loses things (for example, schoolwork, pencils, books, tools, or toys).

Defiance/Aggression (14 Items)

16. Bullies, threatens, or scares others.
22. Is cold-hearted and cruel.
27. Uses a weapon (for example, a bat, brick, broken bottle, knife, or gun).

30. Starts fights with others on purpose.
39. Physically hurts people.
46. Tells lies to hurt other people.
48. Is angry and resentful.
57. Tries to get even with people.
58. Steals secretly (for example, shoplifting or forgery).
65. Intentionally damages or destroys things that belong to others.
83. Threatens to hurt others.
86. Swears or uses bad language.
94. Actively refuses to do what adults tell him/her to do.
102. Argues with adults.

Peer Relations (6 Items)

10. Does not get invited to play or go out with others.
13. Has no friends.
24. Has trouble keeping friends.
62. Is one of the last to be picked for teams or games.
64. Interacts well with other children. (R)
92. Does not know how to make friends.

DSM-IV-TR Symptom Scales
ADHD Inattentive (10 Items)

2. Is forgetful in daily activities.
28. Avoids or dislikes things that take a lot of effort and are not fun.
35. Does not seem to listen to what is being said to him/her.
47. Doesn't pay attention to details; makes careless mistakes.
68. Does not follow through on instructions (even when he/she understands and is trying to cooperate).
79. Fails to complete schoolwork, chores, or tasks (even when he/she understands and is trying to cooperate).
84. Has trouble organizing tasks or activities.
95. Has trouble keeping his/her mind on work or play for long.
97. Loses things (for example, schoolwork, pencils, books, tools, or toys).
101. Is easily distracted by sights or sounds.

ADHD Hyperactive-Impulsive (11 items)

3. Talks too much.
45. Is constantly moving.
54. Acts as if driven by a motor.
69. Runs or climbs when he/she is not supposed to.
43. Blurts out answers before the question has been completed.
61. Has difficulty waiting for his/her turn.

71. Is noisy and loud when playing or using free time.
93. Leaves seat when he/she should stay seated.
98. Fidgets or squirms in seat.
99. Restless or overactive.
104. Interrupts others (for example, butts into conversations or games).

Conduct Disorder (15 items)

6. Skips classes.
11. Has forced someone into sexual activity.
16. Bullies, threatens, or scares others.
27. Uses a weapon (for example, a bat, brick, broken bottle, knife, or gun).
30. Starts fights with others on purpose.
39. Physically hurts people.
41. Is cruel to animals.
56. Lies to avoid having to do something or to get things.
58. Steals secretly (for example, shoplifting or forgery).
65. Intentionally damages or destroys things that belong to others.
76. Runs away from home for at least one night.
78. Has intentionally set fires for the purpose of causing damage.
89. Has broken into someone else's house, building, or car.
91. Goes out at night even though it breaks the rules.
96. Steals while confronting a person (for example, mugging, purse snatching, or armed robbery).

Oppositional Defiant Disorder (8 items)

14. Loses temper.
21. Blames others for his/her mistakes or misbehavior.
48. Is angry and resentful.
57. Tries to get even with people.
59. Annoys other people on purpose.
73. Is irritable and easily annoyed by others.
94. Actively refuses to do what adults tell him/her to do.
102. Argues with adults.

Indices

Conners 3-P ADHD Index (10 Items)

19. Fidgeting.
35. Does not seem to listen to what is being said to him/her.
47. Doesn't pay attention to details; makes careless mistakes.
67. Inattentive, easily distracted.
84. Has trouble organizing tasks or activities.

88. Gives up easily on difficult tasks.
98. Fidgets or squirms in seat.
99. Restless or overactive.
101. Is easily distracted by sights or sounds.
104. Interrupts others (for example, butts into conversations or games).

Conners 3-P Global Index (10 Items)

19. Fidgeting.
25. Cries often and easily.
29. Mood changes quickly and drastically.
34. Fails to finish things he/she starts.
40. Demands must be met immediately—easily frustrated.
50. Excitable, impulsive.
67. Inattentive, easily distracted.
81. Temper outbursts.
85. Disturbs other children.
99. Restless or overactive.

Each item has responses provided as 0 = Not true at all (Never, Seldom), 1 = Just a little true (Occasionally), 2 = Pretty much true (Often, Quite a bit), 3 = Very much true (Very often, Very frequently).

Items marked with a (R) are reverse scored. The responses will be scored as (4 – item score) when contributing to a raw score.

For each scale except the ADHD Index, raw scores for each scale are calculated as the sum of the item responses (taking into account any reverse scored items).

For the ADHD Index, the item responses are transposed prior to calculating the sum.
For item numbers 19, 47, 67, 84, 99, 101, and 104, the following transposition is made.
If the item response is 0 or 1, then the transposed score = 0.
If the item response is 2 then the transposed score = 1.
If the item response is 3 then the transposed score = 2.

For the item numbers 35, 88, and 98, the following transposition is made.
If the item response is 0 or 1, then the transposed score = 0.
If the item response is 2 or 3, then the transposed score = 2.

In the event of a missing item response, Conners gives the following guidance as to the maximum number of allowable item omissions.

Scale	Total Items	Maximum Allowable Item Omissions
Inattention	10	1
Hyperactivity/Impulsivity	14	2

Scale	Total Items	Maximum Allowable Item Omissions
Learning Problems	9	1
Executive Functioning	9	1
Defiance/Aggression	14	2
Peer Relations	6	1
DSM-IV-TR ADHD Inattentive	10	1
DSM-IV-TR ADHD Hyperactive-Impulsive	11	2
DSM IV-TR Conduct Disorder	15	2
DSM IV-TR Oppositional Defiant Disorder	8	1
Conners 3 ADHD Index	10	1
Conners 3 Global Index	10	1

If there are omitted item responses and the number of omitted item response does not exceed the maximum allowable item omissions, then the raw score will be prorated as:

Prorated Score = (Obtained raw score for scale / Total number of items in scale with a response) * (Total number of Items in the scale). As an example, if the Hyperactivity/Impulsivity has responses for 12 of the 14 items in the scale, then the number of missing responses is less than or equal to the maximum allowable number of omissions. Suppose the sum of the responses provided is 15. Then the prorated score will equal (15/12) * 14 = 17.5.

If the number of omitted item responses exceeds the maximum allowable number noted, the raw scale score will not be calculated.

For all scale scores except the ADHD Index, the raw scores will be converted to age/sex adjusted T-scores according to the scoring manual (Conner, 2008). The T-scores will be used in the statistical analyses.

For the ADHD Index score, the total of the transposed scores (or prorated transposed score, if 1 item response is missing) is given a probability index score according to the following table. The probability score is the probability of a classification of ADHD based on the total transposed score.

Total Transposed Score	Probability (%)
0	11
1	29
2	41
3	51
4	56
5	64

Total Transposed Score	Probability (%)
6	71
7	77
8	82
9	87
10	91
11	94
12	97
13	98
14	99
15	99
16	99
17	99
18	99
19	99
20	99

The probability score for the ADHD Index will be used in the statistical analysis.

For the Conners 3-P scale scores, the same methodology, described for the ADHD RS-IV Total in section 11.1, will be used for this analysis. The analysis will be performed using the ITT population.

11.5. WEISS FUNCTIONAL IMPAIRMENT RATING SCALE – PARENT REPORT (WFIRS-P)

The WFIRS-P is an ADHD-specific instrument completed by the parent/legal guardian to evaluate domains of daily functioning that are likely to be impaired in ADHD. The WFIRS-P comprises 50 items used to provide measures of impairment in 6 domains (family, learning and school, life skills, child's self-concept, social activities and risky activities) and overall (total score). The items relate to the period since the last visit and are scored using a 4-point Likert scale: 0 (never or not at all); 1 (sometimes or somewhat); 2 (often or much); or 3 (very often or very much). The instrument is completed at Week 0, Week 14, and Week 26 or ET.

The WFIRS-P domain scores for each patient were the mean of the items in each domain, or of all the items for total score, omitting items with a missing or 'not applicable' score. WFIRS-P domain or total scores were considered invalid if more than 30 % of the item scores used for calculation were missing or 'not applicable' (with the exception of one question relating to siblings, for which a score of 'not applicable' could contribute to the minimum number of items).

For the WFIRS-P total score and domain scores, the same methodology used for the ADHD RS-IV HV Total score described in section 11.1 will be used for this analysis.

Frequency summaries of the count of items with a response of 2 or 3 will also be done by DB treatment group (and overall), and visit.

11.6. SUBGROUP ANALYSIS

Subgroup analyses of the ADHD RS-IV HV total score will be conducted using the following subsets of the ITT population:

- Gender: Male and Female
- Race Group: White, Black or African American, Asian, and Other
- DB Study Age Group (6-9 years, 10-12 years)
- DB Baseline Study BMI category: Underweight (< 5 percentile), Normal (≥ 5 - < 85 percentile), Overweight (≥ 85 - < 95 percentile), Obese (≥ 95 percentile)

12. SAFETY

The safety will be assessed on the basis of study agent exposure, adverse events, clinical laboratory data, ECG parameters, vital signs, physical examinations, neurological examinations, Tanner Staging, Children's Sleep Habit's Questionnaire (CSHQ), and Columbia – Suicide Severity Rating Scale (C-SSRS) Children's Assessment.

All safety data listings will be presented by subject and visit for all enrolled subjects.

The safety data summarizations will be performed in the safety population.

12.1. ADVERSE EVENTS (AEs)

The summary of AEs (or SAEs) will be limited to TEAEs. A TEAE is any AE (or SAE) occurring on or after the date of the first dose of study drug in the SEP360-310 study. All AEs will be coded using MedDRA version 19.0.

TEAEs will be further divided into:

1.) Those events with onset between the date of the first dose of study drug in the SEP360-310 study and 3 days after the last dose of study medication in SEP360-310, inclusive. These will be called on treatment events.

2.) Those events with onset more than 3 days after the last dose of study medication in SEP360-310. These will be called post-treatment events.

AEs with preferred terms of "Insomnia", "Initial insomnia", "Middle insomnia", or "Terminal insomnia", or AEs with Higher Level Term of "Disturbances in initiating and maintaining sleep" will be presented on AE tables in a combined term called "Combined insomnia" with the individual preferred terms within the combined term directly underneath.

All TEAEs will be summarized by SOC and PT. Though only TEAEs will be included in the summary tables, all AEs will be included on the listings (non-TEAEs will be flagged).

An overall summary table of TEAEs by DB treatment will be produced for the following categories:

- Number and percentage of subjects with a TEAE
- Number and percentage of subjects with a treatment-related TEAE
- Number and percentage of subjects with a TEAE leading to discontinuation
- Number and percentage of subjects with a Treatment-related TEAE leading to discontinuation
- Number and percentage of subjects with a serious TEAE
- Number and percentage of subjects with a serious TEAE leading to discontinuation
- Number and percentage of subjects with a treatment-related serious TEAE
- Number and percentage of subjects with a Treatment-related serious TEAE leading to discontinuation
- Number and percentage of subjects with a TEAE leading to death

This overall summary will be repeated for each onset period. For the post-treatment events, the denominators will be the number of subjects in each DB treatment group whose end of study visit was more than 3 days after the last dose date.

Subgroup analyses of the above noted TEAE categories will be produced for the following subgroups (sex, race (categorized as White, Black or African American, Asian, and Other), DB baseline age group (6-9 vs. 10-12 years)).

Adverse events will be summarized by DB treatment and overall for subjects in the safety population. The following summaries of AEs will be provided:

- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs by PT (≥ 3% in any DB treatment group)
- Serious TEAEs by SOC and PT
- TEAEs leading to discontinuation by SOC and PT
- TEAEs by SOC and PT and maximum severity. Missing severity, if any, will be assumed as 'severe'.

- TEAE by relationship to study treatment (related or not related) by SOC and PT. Missing relationships, if any, will be assumed to be 'related'.

- Treatment related SAEs by SOC and PT

The prevalence of Insomnia by study day in the study will be presented graphically by DB treatment and overall. Combined insomnia events will be used for this analysis. On any study day, the numerator will be the number of subjects who were experiencing insomnia (noting that subjects may have experienced multiple episodes during the study), and the denominator will be the number of subjects remaining on open-label study drug treatment.

The following listings of AEs will be provided:

- All AEs

- Adverse events leading to discontinuation of study drug

- Serious adverse events

In the summary tables subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. If a subject has the same AE on multiple occasions, the highest severity (severe, moderate, mild) recorded for the event will be presented and the highest drug relationship (1 = 'Unrelated', 2 = 'Unlikely to be Related', 3 = 'Possibly Related', 4 = 'Probably Related', 5 = 'Related'), reclassified into Related ('Possibly Related', 'Probably Related', 'Related') or Not Related ('Unrelated' and 'Unlikely to be Related'), will be presented on the respective tables. Percentages are based on the number of subjects in the safety population.

12.2. LABORATORY EVALUATIONS

The following laboratory tests are planned to be performed:

HEMATOLOGY: (Differential reported as % and absolute value)

Hemoglobin, Hematocrit, Platelet Count, red blood cell (RBC) count, white blood cell (WBC) - total count, WBC differential reported as % and absolute values to include basophils, eosinophils, lymphocytes, monocytes, neutrophils.

BLOOD CHEMISTRIES:

Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO_3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Magnesium

(Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

URINALYSIS:

Blood, Glucose, Ketones, Leukocyte Esterase, Microscopic Examination, Nitrites, pH, Protein

THYROID PANEL:

Free T3, Free T4, Thyroid stimulating hormone (TSH)

LIPID PANEL:

LDL-Cholesterol, HDL-Cholesterol, Total Cholesterol, Triglycerides

SEX HORMONES:

For females: estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH).

For males: testosterone.

URINE DRUG SCREENING:

Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone, Tricyclic Antidepressants

OTHER TESTS:

Breath Alcohol Test, Serum Pregnancy (ß-hCG) (in female subjects only), Urine Pregnancy Test (in female subjects only)

Hematology, chemistry, urinalysis, thyroid panel, lipid panel, and sex hormones are collected at Open-label baseline, Week 14, Week 26 or ET, and the EOS Visit.

The laboratory results collected in conventional units will be converted to SI units, and the SI units will be used for all of the summaries and listings. Clinical laboratory test results (hematology, chemistry, urinalysis, thyroid panel, lipid panel, and sex hormones) and their changes from DB baseline and OL baseline will be summarized by DB treatment and overall, and by visits including the endpoint (Week 26 LOCF), using descriptive statistics. For hematology, chemistry lipid panel, thyroid panel, and sex hormone tests, result will also be categorized as “Normal”, “Low”, or “High” based on their normal ranges. For urinalysis results, tests will be classified as “Normal” or “Abnormal”. Shift tables comparing laboratory test results from baseline to Week 26

LOCF will be presented. Percentages are based on the number of the safety subjects in a high, low or normal category with non-missing values for both baseline and post-baseline at the given visit.

In addition, the markedly abnormal post-baseline laboratory results will be summarized for certain laboratory tests.

Summaries will be presented separately for hematology and chemistry for subjects with at least one markedly abnormal value during the open-label treatment period. A listing of all markedly abnormal results will be provided.

The criteria for markedly abnormal values are defined below.

Parameter (Unit)	**Markedly Abnormal Range (Conventional Unit)**	**Conversion Factor (Conventional to SI) / SI unit**	**SI Unit Markedly Abnormal Range**
Hematology			
Hemoglobin (g/dL)	Female: ≤ 9.5, Male: ≤ 11.5 ≥ 17.2	10 / g/L	Female: ≤ 95 g/L, Male: ≤ 115 g/L, ≥ 172 g/L
Hematocrit (fraction, %)	≤ 30, ≥ 50	0.01 / (fraction of 1)	≤ 0.30, ≥ 0.50 (1)
WBC (10^3/µL)	≤ 2.8, ≥ 16	1 / x10^9/L (PPD Conv unit K/cu mm)	≤ 2.8, ≥ 16
RBC (10^6/µL)	≤ 3.0, ≥ 6.0	1 / x10^{12}/L (PPD Conv unit x10^6/cu mm)	≤ 3.0, ≥ 6.0
Platelet Count (10^3/µL)	≤ 100, ≥ 500	1 / x10^9/L (PPD Conv unit K/cu mm)	≤ 100, ≥ 500
Eosinophils (%)	≥ 10	1 / %	≥ 10

Parameter (Unit)	Markedly Abnormal Range (Conventional Unit)	Conversion Factor (Conventional to SI) / SI unit	SI Unit Markedly Abnormal Range
Neutrophils (%)	≤ 15	1 / %	≤ 15
Clinical Chemistry			
ALP (U/L)	≥ 3 x ULN	1 / U/L	≥ 3 x ULN
ALT (U/L)	≥ 2 x ULN	1 / U/L	≥ 2 x ULN
AST (U/L)	≥ 2 x ULN	1 / U/L	≥ 2 x ULN
Total Bilirubin (mg/dL)	≥ 2.0	17.1 / mcmol/L	≥ 34.2
Albumin (g/dL)	< 50% LLN	10 / g/L	< 50% LLN
Creatinine (mg/dL)	≥ 2.0	88.4 / mcmol/L	≥ 176
Creatine Phosphokinase (CPK) (U/L)	≥ 450	1 / U/L	≥ 450
LDH (U/L)	≥ 3 x ULN	1 / U/L	≥ 3 x ULN
GGT (U/L)	≥ 150	1 / U/L	≥ 150
Sodium (mEq/L)	≤ 130, ≥ 150	1 / mmol/L	≤ 130, ≥ 150
Potassium (mEq/L)	≤ 3, ≥ 5.5	1 / mmol/L	≤ 3, ≥ 5.5
Bicarbonate (mEq/L)	< 18, > 30	1 / mmol/L	< 18, > 30
Calcium (mg/dL)	< 8.4, or > 11.5	0.25 / mmol/L	< 2.1, or > 2.8

Parameter (Unit)	Markedly Abnormal Range (Conventional Unit)	Conversion Factor (Conventional to SI) / SI unit	SI Unit Markedly Abnormal Range
Chloride (mEq/L)	< 90, > 115	1 / mmol/L	< 90, > 115
Blood Urea Nitrogen (mg/dL)	≥ 30	0.357 / mmol/L	> 10.7
Glucose (fasting) (mg/dL)	≤ 45, ≥ 126	0.05551 / mmol/L	≤ 2.5, ≥11.1
Glucose (random) (mg/dL)	≤ 45, > 200	0.05551 / mmol/L	≤ 2.5, ≥11.1
Lipid Panel (Fasting)			
Total Cholesterol (mg/dL)	≥ 240	0.0259 / mmol/L	≥ 6.2
Triglycerides (mg/dL)	Female: ≥ 170, Male: ≥ 200	0.0113 / mmol/L	Female: ≥ 1.92, Male: ≥ 2.26
HDL-C (mg/dL)	≤ 30	0.0259 / mmol/L	≤ 0.77
LDL-C (mg/dL)	≥ 160	0.0259 / mmol/L	≥ 4.14
Urinalysis			
RBC (hpf)	> 15	N/A	> 15
WBC (hpf)	> 15	N/A	> 15
Sex Hormones			

Parameter (Unit)	Markedly Abnormal Range (Conventional Unit)	Conversion Factor (Conventional to SI) / SI unit	SI Unit Markedly Abnormal Range
FSH (mIU/mL)		1 / IU/L	> 4.2, for Females with Tanner Stage = 1
FSH (mIU/mL)		1 / IU/L	> 10.8, for Females with Tanner Stage = 2
FSH (mIU/mL)		1 / IU/L	> 12.8, for Females with Tanner Stage = 3
FSH (mIU/mL)		1 / IU/L	> 11.7, for Females with Tanner Stage = 4
FSH (mIU/mL)		1 / IU/L	> 9.2, for Females with Tanner Stage = 5
LH (mIU/mL)		1 / IU/L	> 0.18, for Females with Tanner Stage = 1
LH (mIU/mL)		1 / IU/L	> 4.7, for Females with Tanner Stage = 2
LH (mIU/mL)		1 / IU/L	> 12.0, for Females with Tanner Stage = 3
LH (mIU/mL)		1 / IU/L	> 11.7, for Females with Tanner Stage = 4
LH (mIU/mL)		1 / IU/L	> 11.7, for Females with Tanner Stage = 5

Listings will be provided for pregnancy tests. No other summarizations of pregnancy tests will be provided.

12.3. BREATH ALCOHOL TEST

Breath alcohol examination will be monitored at Open-Label Baseline, Week 14, and the EOS Visit. The breath alcohol examination data will be presented in a data listing.

12.4. URINE DRUG SCREENING

Urine drug screening tests are collected at Open-Label Baseline, Week 2, Week 6, Week 10, Week 14, Week 18, Week 22, Week 26, and at the EOS. The urine drug screening data will be presented in a data listing.

12.5. 12-LEAD ECG

Assessment of Standard 12-lead ECG are obtained at each clinic assessment during the study. A central ECG Standard 12-lead ECG will record heart rate (HR), PR interval, RR interval, QT interval, Bazett's corrected QT (QTcB), Fridericia's corrected QT interval (QTcF), and QRS duration. The overall ECG assessment will be centrally reported as "Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant" with respect to relevant abnormalities.

Observed results of each ECG parameter, change from DB baseline, and change from OL baseline will be summarized by DB treatment and overall, and by visit using descriptive statistics.

The QTcF and QTcB results will be adjusted as follows:

$QTcF = QT / \sqrt[3]{RR}$

$QTcB = QT / \sqrt[2]{RR}$

Bazett's and Fridericia's corrected QT_c values will be classified as having QT_c prolongation according to the following conditions.

QTc Prolongation
QTc >460 msec

QTc Prolongation
Increase from double-blind baseline QTc ≥ 60 msec
Increase from double-blind baseline QTc ≥ 30 msec
Increase from open-label baseline QTc ≥ 60 msec
Increase from open-label baseline QTc ≥ 30 msec

The number and percentage of subjects with QTc prolongation using either of the two correction methods (Bazett's, Fridericia's) will be summarized by DB treatment and overall, and by visit.

A shift table comparing the overall ECG assessment from baseline to Week 26 or ET, and from baseline to EOS will be presented.

In addition, the markedly abnormal post-baseline ECG results will also be summarized for subjects with at least one markedly abnormal value during the treatment period. The summary will be completed by DB treatment and overall, and age groups (6 - < 8 years, 8 - < 12 years, 12 - < 16 years, and > 16 years), and overall using the age at the time of the individual assessment.

A listing of markedly abnormal values will be provided.

Criteria for markedly abnormal values, used in the SEP360-202 study, are presented in the table below. They will also be used for the SEP360-310 study summary.

ECG parameter (unit)	**Age (years old)**	**Abnormally Low**	**Abnormally High**
HR (bpm)	6 to <8	< 65	> 115
	8 to <12	< 55	> 110
	12 to <16	< 50	> 105
	≥16	< 50	> 100
PR interval (msec)	6 to <8	--	> 160
	8 to <12	--	> 175
	12 to <16	--	> 180
	≥16	--	> 200
QRS interval (msec)	6 to <8	--	> 100
	8 to <12	--	> 105

ECG parameter (unit)	Age (years old)	Abnormally Low	Abnormally High
	12 to <16	--	> 110
	≥16	--	> 120

12.6. PHYSICAL EXAMINATION

Physical examinations are performed at Open-Label Baseline, Week 14, Week 26 or ET, and End of Study. Any clinically significant abnormalities at screening will be recorded on the medical history form. Any new or worsening clinically significant abnormality at all other visits will be recorded as an AE.

12.7. NEUROLOGICAL EXAMINATION

Neurological examinations will be performed at Open-Label Baseline, Week 14, Week 26 or ET, and End of Study.

Each assessment (i.e. Cranial Nerves, Motor System, Sensory System, Reflexes, Coordination, Gait and Rhomberg's test) will be summarized using summary statistics for categorical variables (normal/abnormal) at each visit by treatment and overall. All percentages will be based on the number of safety subjects in each DB treatment group.

Shift table for baseline condition vs. the worst result during the treatment period (Abnormal > Normal) will be produced by DB treatment and overall. Percentages will be based on the number of subjects in the safety population. The number of subjects without an assessment at the visit will be noted on the shift table.

12.8. VITAL SIGNS

Vital signs (blood pressure, pulse rate, height, height WHO z-score, weight, BMI, BMI z-score, respiratory rate, and oral temperature) will be monitored at every clinic visit. Respiratory rate and oral temperature will be measured following 5 minutes of supine rest.

At any clinic assessment, orthostatic hypotension (determined by blood pressure measurements only) is defined as having either a ≥ 20 mmHg reduction from supine to standing position in systolic blood pressure (SBP) or ≥ 10 mmHg reduction from supine to standing position in diastolic blood pressure (DBP) or both. Orthostatic tachycardia is defined as heart rate increase ≥ 20 bpm from supine to standing position.

Observed values, change from DB baseline, percent change from DB baseline, change from OL baseline, percent change from OL baseline for each vital sign parameter. will be summarized at each visit by DB treatment and overall.

In addition, the markedly abnormal post-baseline vital signs results will also be summarized for subjects with at least one markedly abnormal value during the treatment period. A listing will be provided for all markedly abnormal vital signs. A shift table will be presented comparing shifts from the baseline visit to Week 26 LOCF. Percentages will be based on the number of safety subjects with a non-missing value for both the baseline and post-baseline visit for the given vital sign. A shift table for BMI classification will also be presented comparing shifts from the baseline visit to Week 26 LOCF.

Parameter (unit)	**Age (years old)**	**Markedly Low**	**Markedly High**
SBP (supine, standing) (mmHg)	6-12	Value ≤ 70 and≥ 20 decrease from baseline	Value ≥ 120 and ≥ 20 increase from baseline
	13-18	Value ≤ 90 and ≥ 20 decrease from baseline	Value ≥ 135 and ≥ 20 increase from baseline
DBP (supine, standing) (mmHg)	6-12	Value ≤ 40 and ≥ 15 decrease from baseline	Value ≥ 80 and ≥ 15 increase from baseline
	13-18	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 90 and ≥ 15 increase from baseline
Pulse rate (supine, standing) (bpm)	6-10	Value ≤ 60 and ≥ 15 decrease from baseline	Value ≥ 135 and ≥ 15 increase from baseline
	11-18	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 120 and ≥ 15 increase from baseline
SBP orthostatic criteria (mmHg)	~	≥ 20 decrease from supine to standing position	NA
DBP orthostatic criteria (mmHg)	~	≥ 10 decrease from supine to standing position	NA
Pulse rate orthostatic criteria (bpm)	~	NA	≥ 20 increase from supine to standing position

Temperature (˚C)	~	NA	Value ≥ 38.3˚C and ≥0.8˚C increase from baseline

Note: ~ means that the abnormal range is applicable for all subjects within age group: 6 to 17 years old.

Vital signs data will be provided in a data listing.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment that evaluates suicidal ideation and behavior.

This study will utilize the "Since Last Visit" version of the C-SSRS at each visit.

Subjects will be placed into categories for suicidal ideation and for suicidal behavior based on their responses to various questions.

The Suicidal Ideation categories will be determined as follows by examining the response to the 5 questions under Suicidal Ideation.

Type	Section
Suicidal Ideation	(0) None – if response is No to Questions 1 and 2 (1) Wish to be Dead – if response to Question 1 is Yes and responses to Questions 2-5 are No. (2) Non-Specific Active Suicidal Thoughts – if response to Question 2 is Yes and response to Questions 3-5 are No. (3) Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act – if response to question 3 is Yes and response to questions 4 and 5 are No. (4) Active Suicidal Ideation with Some Intent to Act, without Specific Plan – if response to Question 4 is Yes and response to Question 5 is No. (5) Active Suicidal Ideation with Specific Plan and Intent – if response to Question 5 is Yes.

For suicidal behavior, the following categories will be used. The categories will be determined based on the response to the questions under Suicidal Behavior.

Type	Section
Suicidal Behavior	• Preparatory Acts or Behavior – if response to Preparatory Acts and Behavior is Yes and responses to Actual Attempt, Interrupted Attempt, and Aborted Attempt are No • Aborted Attempt – if response to Aborted Attempt is Yes and responses to Actual Attempt and Interrupted Attempt are No. • Interrupted Attempt – if response to Interrupted Attempt is Yes and response to Actual Attempt is No. • Actual Attempt – if response to Actual Attempt is Yes. • None – if responses to all the above 4 questions are No.

The frequency and percentage by DB treatment and overall, and visit will be summarized for all C-SSRS responses.
Frequency and severity of suicidality using the C-SSRS will be summarized, using a shift table to examine changes in C-SSRS Scores from baseline compared to the worst (highest) category during the treatment period and visit, by DB treatment and overall.

12.10. CHILDREN'S SLEEP HABITS QUESTIONNAIRE (CSHQ)

The CSHQ is a retrospective, 45-item parent questionnaire that is used to examine sleep behavior in young children. The questionnaire is completed at each clinical assessment by the subject's parent or guardian. Each scored question is rated on a 3-point scale as occurring "usually" (i.e., 5–7 times within the past week), "sometimes" (i.e., 2–4 times within the past week), or "rarely" (i.e., never or 1 time within the past week). A number of items on the questionnaire are reverse-scored, so that higher scores

consistently indicate problem behaviors. Ratings are combined to form eight subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness.
The CSHQ will be completed at Open-Label Baseline, and at each scheduled visit through Week 26 or ET.

The questions associated with each subscales are as follows:

Subscale	Question (Item Number)	Reverse Scored
Bedtime Resistance	Child goes to bed at the same time at night (R) (1)	Yes
	Child falls asleep alone in own bed (R) (3)	Yes
	Child falls asleep in parent's or sibling's bed (4)	No
	Child needs parent in the room to fall asleep (5)	No
	Child struggles at bedtime (cries, refuses to stay in bed, etc.) (6)	No
	Child is afraid of sleep alone (8)	No
Sleep Onset Delay	Child falls asleep within 20 minutes after going to bed (R) (2)	Yes
Sleep duration	Child sleeps too little (9)	No
	Child sleeps the right amount (R) (10)	Yes
	Child sleeps about the same amount each day (R) (11)	Yes
Sleep Anxiety	Child needs parent in the room to fall asleep (5)	No
	Child is afraid of sleeping in the dark (7)	No
	Child is afraid of sleep alone (8)	No
	Child has trouble sleeping away from home (visiting relatives, vacation, etc.) (21)	No

Subscale	Question (Item Number)	Reverse Scored
Night Wakings	Child moves to someone else's bed during the night (parent, brother, sister, etc.) (16)	No
	Child awakes once during the night (24)	No
	Child awakes more than once during the night (25)	No
Parasomnias	Child wets the bed at night (12)	No
	Child talks during sleep (13)	No
	Child is restless and moves a lot during sleep (14)	No
	Child sleepwalks during the night (15)	No
	Child grinds teeth during sleep (your dentist may have told you this) (17)	No
	Child awakens during night screaming, sweating, and inconsolable (22)	No
	Child awakens alarmed by a frightening dream (23)	No
Sleep Disordered Breathing	Child snores loudly (18)	No
	Child seems to stop breathing during sleep (19)	No
	Child snorts and/or gasps during sleep (20)	No
Daytime Sleepiness	Child wakes up by him/herself (26) (R)	Yes
	Child wakes up in negative mood (27)	No
	Adults or siblings wake up child (28)	No
	Child has difficulty getting out of bed in the morning (29)	No
	Child takes a long time to become alert in the morning (30)	No
	Child seems tired (31)	No
	Appeared very sleepy or fallen asleep Watching TV (32)	No
	Appeared very sleepy or fallen asleep Riding	No

Subscale	Question (Item Number)	Reverse Scored
	Car (33)	

A Total Sleep Disturbances score is calculated as the sum of all 33 CSHQ scored questions, and can range from 33 to 99. (Two scored items are counted twice in the calculation of two different subscales).
At any assessment, a missing response to an item associated with a subscale will result in that subscale set to missing. Any missing response to the 33 CSHQ questions will result in a missing Total Sleep Disturbances score.

Summaries of observed values and changes from DB baseline and OL baseline in observed values will be done by DB treatment and overall for each visit using descriptive statistics.

12.11. TANNER SCALE

The Tanner scale is a scale of physical development in children, adolescents, and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, testicular volume, and development of pubic and axillary hair.

The Tanner stage is collected for each subject at OL Baseline, and at the Week 26 or Early Termination visit.

A shift table comparing the baseline stage with the stage at Week 26 or Early Termination will be done by gender, DB treatment and overall. Percentages will be calculated using the number of subjects with an assessment completed at both baseline and EOS.

12.12. PHYSICIAN WITHDRAWAL CHECKLIST (PWC)

The Physician Withdrawal Checklist (PWC) is used to evaluate symptoms of withdrawal after discontinuation of study drug. Symptoms are assessed as present or absent and if present then intensity is assessed as mild, moderate, or severe.

This checklist will be assessed at the end of treatment visit (Week 26) or treatment termination and at the Week 29 or EOS Visit.

The scale includes 20 symptoms. Each symptom is assessed on a 4-point scale using the following:

0=Not Present
1=Mild
2=Moderate
3=Severe

The score for each question is summed to compute a total score ranging from 0 to 60. If the response to any question is missing, then the total score will be missing. The PWC will be summarized using descriptive statistics by visit for the total score. The number and percentage of subjects with a Present response (mild, moderate, or severe) will be provided for each of the 20 PWC items. In addition, responses of moderate or severe will be summarized separately at each visit.

Analyses of the PWC will be repeated by gender subgroups.

12.13. DISCONTINUATION-EMERGENT SIGNS AND SYMPTOMS (DESS) SCALE

The DESS Scale (Rosenbaum-1998) is a clinician-rated instrument of 43 items used to evaluate signs and symptoms associated with discontinuation or interruption of monoamine reuptake inhibitor treatment.

On non-clinic days, the DESS Scale will be completed by site staff during a call to the subject/parent/legal guardian.

The DESS will be assessed at the Week 26 or Early Termination Visit, and then reassessed at Week 27, Week 28, and Week 29 or End of Study.
Each of the 43 signs and symptoms is assessed and placed in one of the following categories: new symptom, old symptom but worse, old symptom but improved, old symptom but unchanged, and symptom not present. Each sign and symptom that is placed in the category new symptom or in the category old symptom but worse receives 1 point. All other categories receive 0 points. The total DESS score is the sum of the number of points, which corresponds to the number of symptoms rated as either a new symptom or as an old symptom but worse. The score ranges from 0 to 43, where higher scores indicate more discontinuation-emergent signs and symptoms. The total score and change from Week 26 will be summarized descriptively separately by visit. For each

symptom, the number and percentage of subjects reporting the symptom as new or worsened will be provided.

Analyses of the DESS will be repeated by gender subgroups.

13. STATISTICS (TO BE INCORPORATED INTO SECTION 16.1.9 OF CSR)

13.1. STATISTICAL METHODS AND ANALYSIS OUTPUTS

13.1.1. Statistical Methods

Statistical Analysis System (SAS) version 9.3 will be used to perform all the statistical analyses in the CSR.

14. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings and figures. INC Research SOPs 03.010.02 and 03.013.02 provide an overview of the development of such SAS programs.

INC Research SOP 03.009.04 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency, and commenting, and by review of the produced output.

15. TABLE AND LISTING SHELLS

15.1. TABLE SHELLS: SEE ATTACHMENT 1

15.2. LISTING SHELLS: SEE ATTACHMENT 2

15.3. FIGURE SHELLS: SEE ATTACHMENT 3

16. REFERENCES

Conners, C.K. Conners' Rating Scales 3rd Edition 2008 - Conners 3 (2014).

Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Randomized Clinical Trial. Biol Psychiatry 1998;44:77–87.

17. APPENDIX 1 – SCHEDULE OF ASSESSMENTS

All assessments will be performed as per the "Schedule of Assessments" copied from the protocol.

	OL Baseline [a]	Treatment Period									Withdrawal Period		
Visit	**1E**	**2E**	**3E**	**4E**	**5E**	**6E**	**7E**	**8E**	**9E**	**10E/ET**	**11E Call**	**12 E Call**	**13E/EOS**
Week		**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 10**	**Week 14**	**Week 18**	**Week 22**	**Week 26 [b]**	**Week 27 [b]**	**Week 28 [b]**	**Week 29 [b]**
Day	**Day 0**	**Day 7 ± 3**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 42 ± 3**	**Day 70 ± 3**	**Day 98 ± 3**	**Day 126 ± 3**	**Day 154 ± 3**	**Day 182 ± 3**	**Day 189 ± 3**	**Day 196 ± 3**	**Day 203 ± 3**
Obtain informed consent/assent	X												
Inclusion/Exclusion criteria	X												
Dispense study drug[c]	X	X	X	X	X	X	X	X	X				
Study drug accountability		X	X	X	X	X	X	X	X	X			
Between visit contact[d]						At the approximate midpoint between Visits 5E and 6E, Visits 6E and 7E, Visits 7E and 8E, Visits 8E and 9E, and Visits 9E and 10E.							
Medical and Psychiatric History	X (carried over)												
Concomitant medication review	X (carried over)	X	X	X	X	X	X	X	X	X			X
Physical Examination	X (carried over)						X			X			X
Neurological Examination	X (carried over)						X			X			X
Height (measured by stadiometer)	X (carried over)	X	X	X	X	X	X	X	X	X			X
Weight (including body mass index)	X (carried over)	X	X	X	X	X	X	X	X	X			X
Vital Signs	X (carried over)	X	X	X	X	X	X	X	X	X			X
Electrocardiogram (ECG)	X (carried over)	X	X	X	X	X	X	X	X	X			X
Adverse Event Monitoring	X (carried over)	X	X	X	X	X	X	X	X	X			X

	OL Baseline [a]	Treatment Period									Withdrawal Period		
Visit	**1E**	**2E**	**3E**	**4E**	**5E**	**6E**	**7E**	**8E**	**9E**	**10E/ET**	**11E Call**	**12 E Call**	**13E/EOS**
Week		**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 10**	**Week 14**	**Week 18**	**Week 22**	**Week 26 [b]**	**Week 27 [b]**	**Week 28 [b]**	**Week 29 [b]**
Day	**Day 0**	**Day 7 ± 3**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 42 ± 3**	**Day 70 ± 3**	**Day 98 ± 3**	**Day 126 ± 3**	**Day 154 ± 3**	**Day 182 ± 3**	**Day 189 ± 3**	**Day 196 ± 3**	**Day 203 ± 3**
Tanner Staging	X (carried over)									X			
Columbia Suicide Severity Rating Scale (C-SSRS) Children's Assessment[e]	X (carried over)	X	X	X	X	X	X	X	X	X			X
Clinical Global Impression – Severity (CGI-S)	X (carried over)	X	X	X	X	X	X	X	X	X			
ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV)	X (carried over)	X	X	X	X	X	X	X	X	X			
Conners 3rd Edition Parent (Conners 3-P)	X (carried over)	X	X	X	X	X	X	X	X	X			
Children's Sleep Habits Questionnaire (CSHQ)	X (carried over)	X	X	X	X	X	X	X	X	X			
Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P)	X (carried over)						X			X			
Physician Withdrawal Checklist (PWC)[j]										X			X
Discontinuation-Emergent Signs and Symptoms (DESS) Scale[j]										X	X	X	X
Hematology/Chemistry	X (carried over)						X			X			X
Thyroid panel[f]	X (carried over)						X			X			X
Lipid panel[g]	X (carried over)						X			X			X

	OL Baseline [a]	Treatment Period									Withdrawal Period		
Visit	**1E**	**2E**	**3E**	**4E**	**5E**	**6E**	**7E**	**8E**	**9E**	**10E/ET**	**11E Call**	**12 E Call**	**13E/EOS**
Week		**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 10**	**Week 14**	**Week 18**	**Week 22**	**Week 26 [b]**	**Week 27 [b]**	**Week 28 [b]**	**Week 29 [b]**
Day	**Day 0**	**Day 7 ± 3**	**Day 14 ± 3**	**Day 28 ± 3**	**Day 42 ± 3**	**Day 70 ± 3**	**Day 98 ± 3**	**Day 126 ± 3**	**Day 154 ± 3**	**Day 182 ± 3**	**Day 189 ± 3**	**Day 196 ± 3**	**Day 203 ± 3**
Sex hormone tests[h]	X (carried over)						X			X			X
Serum β-hCG (in females)[i]	X (carried over)												X
Urinalysis	X (carried over)						X			X			X
Urine drug screen	X (carried over)		X		X	X	X	X	X	X			X
Urine β-hCG (in females)[i]					X	X	X	X	X	X			X
Breath alcohol test	X (carried over)						X						X

18. APPENDIX 2 - PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS®, Release 9.3 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

18.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs.
- One output file can contain several outputs.
- Output files will be delivered in Rich Text Format (RTF) for draft and in PDF format for final.

18.2. TABLE, LISTING, AND FIGURE FORMAT

18.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- Tables and listings will be in black and white (no color), unless otherwise specified. Figures will be provided in color.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

18.2.2. Headers

- All output should have the following header at the top left of each page:

  Sunovion Pharmaceuticals, Inc.

  Protocol SEP360-310

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

18.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). International Conference on Harmonization (ICH) E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis population should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
(<Population Name>)

18.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the DB treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each DB treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a 'All' or 'Total' column (if applicable).

18.2.5. Body of the Data Display

18.2.5.1. Table Conventions

- Units will be included where available.

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category may be added to any parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system,

treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, those terms should then be sorted alphabetically.

- Missing descriptive statistics or p-values which cannot be estimated should be reported as "-" with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed.

- Where a category with a subheading (such as SOC) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

18.2.5.2. Listing Conventions

- Listings will be sorted for presentation in order of double-blind treatment groups as noted in section 6.1, subject number, visit/collection day, and visit/collection time.

- Dates will be printed as recorded on CRF.

- All observed time values must be presented as recorded on CRF.

- Units will be included where available.

18.2.5.3. Figure Conventions

- Unless otherwise specified, for all figures, time will be displayed on the X-axis and endpoint (e.g., overall survival) values will be displayed on the Y-axis.

18.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

- Footnotes should begin with "Note:" if an informational footnote, or 1, 2, 3, or a, b, c etc. if a reference footnote. Each new footnote should start on a new line where possible.

- Footnotes will be used sparingly and must add value to the table, figure, or data listing.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the listing source (only for table outputs) and the date the output was produced.

Cross-reference: Listing xx.x
Program: Txxxxxx.sas <date>

19. APPENDIX 3 – HANDLING PARTIAL/MISSING DATES

19.1. MEDICATION DATE

For prior and concomitant medications with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining if a medication is prior or concomitant only.

- For start dates, if day is missing the first of the month will be used. If month is missing January will be used. If the start date is completely missing, the date of first dose will be used. If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

- For stop dates, if the day is missing then the last day of the month will be used. If the month is missing then December will be used. If the stop date is completely missing then the date of last dose will be used. If the start date is complete and the imputed stop date is earlier than the actual start date, the stop date will be imputed as the start date.

Both prior and concomitant medications are collected on the same CRF page, the following rules will be used to distinguish prior versus concomitant medication:

- Medications with a start date prior to the first date of study drug will be considered prior medications.

- Medications with a start date on or after the first date of study drug will be considered concomitant medications.

- Medications that are ongoing are considered concomitant medications.

19.2. ADVERSE EVENT DATE

If the adverse event start date is partially or completely missing, then the following rules will be used to impute the start date for the purposes of determining the treatment emergence of adverse events. .

- If the start day is missing then the first day of the month will be used.

- If the start month is missing then January will be used.

- If the start date is completely missing then the date of first dose will be used.

- If the end date is complete and the imputed start date is after the end date, then the start date will be imputed as the end date.