STATISTICAL ANALYSIS PLAN

A Randomized, Multicenter, Double-blind, Placebo-controlled, Parallel-group Efficacy and Safety Study of Dasotraline in Children Aged 6 to 12 Years with Attention-Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom Setting

Protocol SEP360-305

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1.0	28 February 2017	Original SAP (Note: SAP version 1.0 includes revisions from Protocol Amendment 1.0 and 2.0. Protocol Amendment 2.0 resulted in the discontinuation of the 6 mg/day dose of dasotraline.)

APPROVALS

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LIST OF ABBREVIATIONS

Commonly used abbreviations (such as units and abbreviations used for electrocardiogram assessments) are not included in this list.

Abbreviation	*Definition*
ADHD	attention deficit hyperactivity disorder
ADHD-RS-IV HV	ADHD Rating Scale Version IV Home Version based on DSM-IV criteria
AE(s)	adverse event(s)
AIC	Akaike information criterion
ANCOVA	analysis of covariance
ATC	Anatomic Therapeutic Chemical
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
EOS	End of Study
ICH	International Conference on Harmonisation
ITT	intent-to-treat
LS Mean	least-squares mean
MAPLV	Markedly abnormal post-baseline values
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation

Abbreviation	*Definition*
PCS	potentially clinically significant
PERMP	Permanent Product Measure of Performance
PERMP-A	PERMP-number of PERMP problems attempted
PERMP-C	PERMP-number of PERMP problems correctly completed
PMM	pattern mixture model
PP	per protocol
PT	preferred term
RBC	red blood cell
ROC	Receiver Operating Characteristic
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SKAMP	Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale
SKAMP-CS	SKAMP-Combined Score
SOC	system organ class
TEAE	treatment-emergent adverse event
WBC	white blood cell
WHO	World Health Organization
WHO DRUG E	World Health Organization – Enhanced Drug Dictionary

1. PURPOSE OF THE STATISTICAL ANALYSIS PLAN

The purpose of the analyses described in this document is to compare the safety and efficacy of dasotraline to placebo in pediatric patients with attention deficit hyperactivity disorder (ADHD).

The statistical analysis plan (SAP) is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials [1] and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports [2].

This SAP describes the populations that will be analyzed, the subject characteristics parameters, the efficacy parameters, and the safety parameters. The details of the specific statistical methods that will be used will be provided. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report (CSR). Table, figure, and listing specifications are provided in separate documents.

2. PROTOCOL SUMMARY

2.1 Study Objectives

The primary objective of this study is to evaluate the efficacy of dasotraline compared to placebo on attention-deficit hyperactivity disorder (ADHD) symptoms in children (6 – 12 years of age) in a laboratory classroom setting.

The secondary objectives are to evaluate the efficacy of dasotraline compared to placebo on ADHD symptoms throughout the day (12 to 24 hours post-dose) in children in a laboratory classroom setting and to evaluate the safety and tolerability of dasotraline using physical examinations, 12-lead electrocardiograms (ECG), vital signs, adverse event (AE) reports, clinical laboratory results, and Columbia – Suicide Severity Rating Scale (C-SSRS) Children's Assessment.

2.2 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study in children with ADHD in a laboratory classroom setting. The study will target 110 subjects (55 per treatment group) in an attempt to have 100 subjects complete the study.

The study will be comprised of 3 periods:

1. Period 1: Screening (up to 35 days) including a 3 - 5 day ADHD medication washout prior to Day -1;

2. Period 2: Double-blind randomized treatment with either dasotraline 4 mg/day or placebo for 14 days (prior to Protocol Amendment 2.0, subjects were also randomized to dasotraline 6 mg/day); and

3. Period 3: End of Study (EOS) Visit (7 days after last dose)

Prior to the start of treatment (Day 1) and following the conclusion of the 14-day double-blind period (Day 15), subjects will undergo a full-day laboratory classroom evaluation during which approximately 12 to 18 subjects will be assessed. Each laboratory classroom day will include seven 30-minute simulated classroom sessions where trained observers will assess subjects using the Swanson, Kotin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale. In addition during each classroom session, a 10-minute math test (Permanent Product Measure of Performance [PERMP]) will be administered to evaluate sustained attention and effort. The appropriate math level for each subject is determined based on results of the math pretest administered at screening.

The primary efficacy endpoint will be baseline (Day 1) to endpoint (Day 15) change in the SKAMP Combined score (SKAMP-CS).

Safety and tolerability will be monitored throughout the study by physical and neurological examinations, 12-lead ECG, vital signs, AEs, clinical laboratories (hematology, chemistry, and urinalysis), and C-SSRS.

Screening: The screening period will be completed within a maximum of 35 days prior to the first dose of study drug and will begin with acquisition of informed assent by the subject and informed consent from at least one of the subject's parents/legal guardians.

Subjects will be confirmed to have been treated with a methylphenidate for at least 6 weeks prior to Day -7. Subjects will be evaluated by the investigator and confirmed to demonstrate adequate clinical response to prior treatment with methylphenidate based on clinical assessment and informant interview, as well as, review of available medical records. Between Days -9 and -7, the subject's parent/legal guardian will be contacted to complete the ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV), or if the parent/legal guardian cannot be reached, it may be completed when he or she brings the subject on Day -7. On Day -7 subjects will attend a half-day practice laboratory classroom session intended to familiarize them with classroom schedules and procedures related to SKAMP evaluations, PERMP tests, and other planned activities. All subjects will discontinue prior methylphenidate treatment for 3-5 days prior to Day -1 in order to ensure that there is at least a 72 hour washout from methylphenidate prior to the assessment of ADHD symptoms on Day -1. The day before randomization, the subject's parent/legal guardian will be contacted by study site staff in order to confirm clinical worsening of the subject's ADHD symptoms since discontinuation of methylphenidate. Clinical worsening is defined as an ADHD-RS-IV HV total score ≥ 26 and demonstration of at least a 30% worsening in ADHD-RS-IV HV total score since the last assessment and following the minimum 72 hour washout from prior methylphenidate treatment. Subjects who do not demonstrate clinical worsening following washout of methylphenidate will be considered screen failures and not randomized.

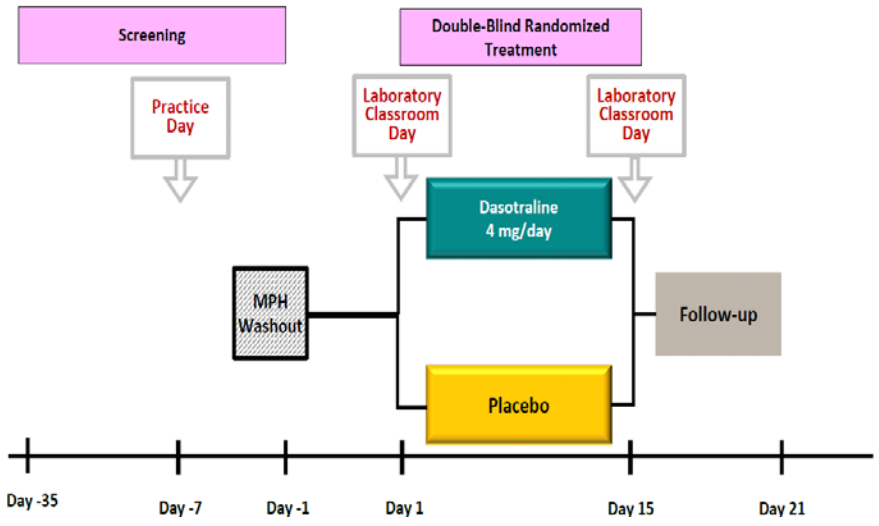
Double-blind Period: On Day 1 subjects will return to the clinic in the morning and those who meet all inclusion and no exclusion criteria will be randomized (1:1) to receive 4 mg/day dasotraline or placebo and will attend classroom sessions in which they will be evaluated for ADHD symptoms using the SKAMP assessment. During this baseline classroom assessment (Day 1), subjects will be evaluated at regular intervals: approximately 8 AM, 10 AM, 12 PM, 2 PM, 4 PM, 6 PM, and 8 PM. Subjects will begin taking study drug on the evening of Day 1 (with

or without food) and take one dose each evening before bedtime for a total of 14 days. Study drug should be taken at approximately the same time each evening. The first dose of study drug may be administered in the clinic before the subject leaves or at home. On the night (Day 14) before the second classroom day, study drug must be taken at 8 PM plus or minus 30 minutes. During the double-blind period, the clinical site will attempt to contact the subject's parent/legal guardian daily with a reminder to administer study drug. A dosing diary will be provided to the parent/legal guardian to record the date and time of each administration of study drug. On Day 15 subjects will return to the clinic in the morning and classroom sessions will be started at approximately 8 AM, 10 AM, 12 PM, 2 PM, 4 PM, 6 PM and 8 PM to coincide with 12, 14, 16, 18, 20, 22, and 24 hours following the Day 14 dose.

End of Study: Seven (± 2) days after the last dose of study drug, all subjects will return to the clinic complete assessments. After the EOS visit, all subjects will be referred for continuation of their care as determined by the investigator. Additionally, for subjects who complete the study or discontinue for tolerability or lack of efficacy reasons, the sponsor will provide support for approved ADHD medication costs for up to 3 months after participation in the study, if deemed medically appropriate by the subject's healthcare provider.

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in Appendix 14.1, Schedule of Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit. The timing of events during a sample laboratory classroom day is provided in Appendix 14.2.

Figure 1: Study Schematic



2.3 Study Population

The subject population includes males and females ranging from 6 to 12 years of age, and in concert with standard practice guidelines, will be required to have a diagnosis of ADHD established by a comprehensive psychiatric evaluation that reviewed Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD (inattentive, hyperactive, or combined presentation). The specific inclusion and exclusion criteria can be found in the protocol, Sections 8.1 and 8.2.

2.4 Method of Assigning Subjects to Treatment Groups

After successfully meeting study entry criteria, subjects will be randomly assigned in a 1:1 ratio to 1 of the 2 following treatments:

- 4 mg/day dasotraline (N = approximately 55 subjects)
- Placebo (N = approximately 55 subjects)

Under previous versions of the protocol, subjects were also randomly assigned to a third treatment group in a 1:1:1 overall ratio: 6 mg/day dasotraline (N = approximately 20 subjects randomized before protocol was amended). An Interactive Response System (IXRS) will be used to manage randomization on Day 1 and, if necessary, for emergency unblinding of treatment assignment during the study. The IXRS is an integrated web based subject and drug management system.

Study medication will be assigned by an IXRS based on the randomization schedule. The IXRS will generate instructions on which medication number to assign to a subject.

2.5 Treatment Regimens

Under supervision from the subject's parent/legal guardian, subjects will self-administer the study drug on an outpatient basis for 14 days beginning the evening of Day 1. Study drug will be taken at approximately the same time each evening. The first dose of study drug may be administered in the clinic before the subject leaves or at home. On Day 14, the night before the second classroom day, study drug must be taken at 8 PM plus or minus 30 minutes. All study medication doses will consist of one 4 mg or placebo capsule per day taken by mouth.

2.6 Sample Size Determination

A post-baseline least square (LS) mean of 18.66 in mean SKAMP-CS obtained from an average of 7 assessments collected across the 12-hour classroom day was observed for the placebo group in a similarly designed study (Wigal 2013) [3]. It is assumed that the dasotraline group will have approximately 20% improvement in mean SKAMP-CS

for dasotraline 4 mg/day versus placebo. The treatment mean difference in change from baseline is therefore assumed to be 4.0 units (effect size of 0.8) versus placebo on mean SKAMP-CS with a common standard deviation of 5 units for dasotraline 4 mg/day. The two-sample t-test with equal variance procedure using nQuery Version 7.0 was utilized for the sample size/power calculation. A total of 100 subjects (50 each for the dasotraline 4 mg/day and placebo groups) will provide at least 95% power to detect statistically significant treatment differences for the dasotraline dose group versus placebo in the primary endpoint at a 5% significance level (2-sided).

The study will target approximately 110 subjects randomized in an attempt to have 100 subjects complete the trial. In addition, approximately 20 other subjects were randomized to dasotraline 6 mg/day under previous versions of the protocol. The total number of subjects randomized in this study will be approximately 130.

3. GENERAL ANALYSIS, REPORTING, AND PROGRAMMING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies may be given in the specific detailed sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

All continuous study assessments will be summarized by treatment group (4 mg/day dasotraline, 6 mg/day dasotraline, combined dasotraline [4 mg/day + 6 mg/day], and placebo) and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment group and time point (as applicable) using frequency counts and percentages. All study data will be listed by subject, treatment group, and time point (as applicable).

Hypothesis testing, unless otherwise indicated, will be 2-sided and performed at the 5% significance level. When confidence intervals are presented, they will be 2-sided with a confidence coefficient of 95%. P-values will be reported to 3 decimal places if greater than 0.001. If less than 0.001, '<0.001' will be displayed. P-values and significance levels will be reported as 0.05 rather than .05. Due to the removal of the 6 mg/day dasotraline treatment group from the study under Protocol Amendment 2.0, the hypothesis testing of 6 mg/day dasotraline versus placebo will be conducted as an exploratory analysis only and will be summarized separately from the 4 mg/day treatment group.

Data will be summarized based on the recorded visit; no visit windowing will be performed.

No preliminary rounding will be performed; rounding will only occur after analysis. To round, the digit to right of last significant digit will be considered: if <5 then round down, if ≥5 then round up. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. Minimums and maximums will be presented with the same precision as the original data.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0. Medications will be coded with the World Health Organization – Enhanced Drug Dictionary (WHO DRUG E, 2016 Q1 version).

All analyses will be performed using the SAS System® version 9.3 or higher.

The following general programming conventions will apply:

Exposure days: (Last dosing date – first dosing date + 1)

Compliance: [(Number of doses taken)/(number of doses planned)]*100

Duration days: (End/resolution date – start/onset date +1)

Study day: (Date of interest – first dosing date + 1) if date of interest is on or after the first dosing date. (Date of interest – first dosing date) if date of interest is before the first dosing date.

4. ANALYSIS POPULATIONS

The 3 analysis populations are defined below. Subjects will be analyzed based on the treatment to which they are randomly assigned. Identification of the subjects to be included in each analysis population will be determined prior to database unblinding. The database will be locked and unblinded after the SAP is signed and authorized, there are no outstanding data issues, and the final analysis populations are imported into the study database.

4.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all subjects who are randomized. The ITT population will be used for the efficacy analyses. Efficacy data will be analyzed according to the treatment the subject was randomized to receive.

4.2 Safety Population

The safety population includes all subjects who are randomized and receive at least 1 dose of study medication. All safety analyses will be performed using the safety population, which includes subjects that had been treated with dasotraline 6 mg/day.

Safety data will be analyzed according to the treatment the subject actually received, regardless of the treatment to which the subject was originally randomized. For subjects who inadvertently received treatment from more than one treatment arm due to site conduct error, the subject will be categorized by the treatment he/she received the most.

4.3 Per-Protocol Population

The per-protocol (PP) population is defined as all subjects from the ITT population without any important protocol deviations (see Section 4.5). This supplemental efficacy population will be used to assess robustness of the primary analysis results.

4.4 Disposition of Patients

Subject disposition will be summarized for all screened subjects, for each treatment group and overall. The following subject disposition information will be presented:

- The number and percentage of patients who were screened, who were screen failures, who were randomized, who completed the study, and who prematurely discontinued from the study

- The number and percentage of patients who discontinued prematurely, by reason for premature discontinuation

- The number and percentage of patients in the ITT, safety, and PP populations

In addition to these summaries, a listing by subject will be provided that shows treatment assignment, patient number, sex, age, race, reason for discontinuation, and any specific comments related to discontinuation.

4.5 Protocol Deviations

Protocol deviations (PDs) will be collected during monitoring visits. Protocol deviations will be placed, but not limited to, into the following categories: prohibited concomitant medications, dosing, enrollment inclusion/exclusion criteria, laboratory, non-compliance, and others which are deemed to be study PDs. Each instance of a PD will be reviewed and determined to be important or minor before the study DBL.

A summary of important PDs will be provided as number (%) of subjects with at least 1 important PD and number (%) of subjects in each category in all randomized subjects. A listing by subject will also be provided that will include all PDs, deviation date, type, and any specific comments related to the deviation.

The following conditions, if met, would constitute an important PD. As such, any subject meeting one or more of these conditions would be omitted from the PP population. Important PDs are not limited to the list below. All protocol deviations within the monitoring report and the clinical database will be reconciled and adjudicated by the clinical team after the study is complete for the identification of all other important PDs.

	Category	Explanation
1	No proof of randomization or subjects mistakenly randomized	At Visit 4, there is no randomization number indicated on CRF field or subject mistakenly assigned randomization number.
2	Subject is non-compliant	Subject is not lost to follow-up and is <75% or >125% compliant with study drug at any point in the study.
3	Prohibited medications taken	Subject took any of the prohibited medications listed in Section 10.3.1 of the protocol during the study from screening through the EOS visit, unless the medication is clinically adjudicated as permissible.
4	Treated subject who did not meet inclusion/exclusion	Subject failed one or more of the inclusion or exclusion criteria listed in Section 8 of the

	criteria	protocol, but continued in the double-blind period of the study.
5	Subject tests positive for substance abuse	Subject has one or more positive urine drug screen test at any visit during the course of the study.
6	Subject is unblinded during study	Subject is unblinded to treatment at any time during the course of the study.
7	Subject receives incorrect treatment	Subject's actual treatment received does not match randomized planned treatment.

5. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics including sex, race, ethnicity, age (both continuous and categorized: 6-9 years and 10-12 years), baseline weight (kg), height (cm), and BMI (kg/m^2) will be summarized by treatment group and overall for the safety and ITT populations. Sex, race, age group, and ethnicity will be summarized using summary statistics (n and percentage) for categorical variables. Age, baseline height, baseline weight, and baseline BMI will be summarized using summary statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables. Demographic and baseline characteristics will also be provided in a listing by subject.

5.1 Prior, Concomitant, and Post-Treatment Medications

Prior medications are defined as the following:

- Medications with a start date prior to the first date of study drug.

Concomitant medications are defined as the following:

- Medications with a start date prior to the first date of study drug and with a stop date after the first date of study drug, or
- Medications with a start date prior to the first date of study drug and is ongoing, or
- Medications with a start date on or after the first date of study drug.

Post treatment medications are defined as the following::

- Medications with a start date after the last dose of study drug, or
- Medications with a start date on or prior to last date of study drug and is ongoing, or
- Medications with a start date on or prior to last date of study drug and stop date after last date of study drug

All medications will be coded using World Health Organization drug dictionary (WHO DRUG E, 2016 Q1 version). Medications with partial start and/or end dates will be described as prior, concomitant, or post-treatment medications by using available non-missing information. Medications with completely missing start dates (i.e., missing information for medication start day, month, and year) are assumed to be both prior and concomitant medications.

The frequency and percentages of subjects using prior, concomitant, and post-treatment medications at any stage of the study will be summarized according to the WHO-DD Anatomical Therapeutic Chemical (ATC) classification Level 2 and preferred

term, by treatment group for the safety population. The ATC levels will be presented in decreasing order of the total number of subjects (frequency). The ATC levels with the same frequency will be presented alphabetically. Preferred terms within each ATC level will be presented in decreasing order of the total number of subjects (frequency). The prior and concomitant medications will also be presented in listings by subject.

5.2 Medical History

Medical history will be coded using MedDRA Version 19.0. The count and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT) will be summarized descriptively by treatment group using the safety population. The SOC terms and PTs will be presented in decreasing order of the total number of subjects (frequency) who experienced each history term. System organ class terms and PTs with the same frequency will be presented alphabetically. Medical history information will also be provided in a listing by subject.

5.3 Psychiatric History

Psychiatric history will be summarized by DSM-5 and diagnosis. The count and percentage of subjects under each DSM-5 code and diagnosis will be summarized by treatment group using the safety population. The summary will be presented in decreasing order of the total number of subjects (frequency) who experienced each psychiatric diagnosis. Psychiatric history information will also be provided in a listing by subject.

6. MEASUREMENT OF TREATMENT COMPLIANCE

Compliance with study drug will be monitored closely and determined at each visit. Subjects and their parent(s)/legal guardian(s) will be instructed to bring all unused study drug with them to the Day 15 visit. Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100. Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant. Treatment compliance (number of missed days) and treatment exposure (e.g. time in trial, time on treatment) will be tabulated overall and by the following groups: <75%, 75%-125%, and >125%. Subjects who are lost to follow-up and/or subjects who do not return unused study drug will have missing compliance data.

Each subject's compliance and treatment exposure data will be listed.

7. EFFICACY EVALUATION

7.1 Overview of Efficacy Analysis Issues

7.1.1 Handling of Dropouts or Missing Data

Missing data could occur under either or both of the following scenarios: (1) missing or invalid data for individual questions in the SKAMP; and (2) missing SKAMP-CS at individual time points. The approach to handling missing data under these scenarios is described below.

7.1.1.1 Missing Individual Items in the SKAMP Scale

The SKAMP scale is a 13-item independent observer rating of subject impairment of classroom observed behaviors. Each item is rated on a 7-point impairment scale (0 = normal to 6 = maximal impairment). The combined scores for the SKAMP are obtained by summing the values of corresponding items in the assessment.

Missing or invalid data for individual questions will be handled by rules specific to the validated SKAMP scale as follows:

- If 3 or more individual items in the SKAMP have missing or invalid data, the SKAMP-CS will be set to missing.
- If 1 or 2 individual items in the SKAMP are missing or invalid, the values for the missing individual items will be imputed using the mean of the non-missing individual items for the particular subject at that visit, rounded to the nearest integer.
- If any item within a SKAMP subscale is missing or invalid, the entire subscale score will be set to missing.

7.1.1.2 Missing SKAMP Combined Scores at Individual Time Points

Primary Analysis

No imputation of missing SKAMP-CS at individual time points will be done for the primary efficacy analysis. Subjects with missing SKAMP-CS data at all individual time points at either the baseline or Day 15 visit will not be included in the primary analysis.

Sensitivity Analyses

To explore the robustness of the primary efficacy analysis of the change from baseline at Day 15 in ADHD symptoms in mean SKAMP-CS, 3 sensitivity analyses of the

primary analysis may be performed: a placebo-based multiple imputation (MI) pattern-mixture model (PMM) analysis and a tipping point analysis using the PMM.

Sensitivity analysis one: Placebo-based MI PMM

To explore the robustness of the primary analysis results, a sensitivity analysis will be carried out that assesses the situation where the data are not missing at random (NMAR). More specifically, all subjects taking dasotraline who discontinue for any reason will be assumed to behave like placebo subjects.

A controlled, multiple imputation approach based on PMM will be applied for those subjects on dasotraline using the 'Copy Reference' approach [4]. More specifically, missing data for those subjects taking dasotraline who discontinued will be imputed based on the posterior distribution of the placebo group. Missing data for placebo subjects who discontinued will also be imputed using the observed values of the placebo group.

Data will be imputed using SAS PROC MI (v9.3 or later) using the full conditional specification method (FCS). Twenty burn-in iterations will be performed prior to each imputation. The imputation model will include clinical site, observed non-missing baseline SKAMP-CS, observed non-missing baseline PERMP scores, age, and sex. One hundred imputed datasets will be generated for analysis.

The same model used in the primary analyses will be fit to each of the 100 datasets. The parameter estimates and standard errors will be combined using PROC MIANALYZE in SAS v 9.3 or higher.

Sensitivity analysis two: Tipping Point Analysis using PMM

The goal of the tipping point analysis is to determine how robust the results of the primary analysis are to varying its assumption that the change from baseline at Day 15 mean SKAMP-CS for subjects that discontinue from the dasotraline group is the same as the completers in the dasotraline group. In particular, this analysis examines how altering this assumption to allow the discontinued subjects to have better and worse outcomes will impact the resulting estimates of the treatment effect. This will quantify the range of values which the assumptions can take on and still provide the same conclusions as the primary analysis, giving a very direct measure of the sensitivity of the primary analysis to deviations from the assumptions using an approach that has missing values for dasotraline discontinuation subjects imputed. Data will be imputed using the same imputation model and methods described in the first sensitivity analysis.

In this analysis, the estimate of the effect in the dasotraline subjects may be viewed as a weighted average of the observed average for dasotraline completers and the

average MAR estimate for dasotroline subjects. This can be approximated as:

(1-p)*[Avg (dasotraline completers)] + (p*Δ*[MAR estimate for dasotraline subjects]),

where p is the proportion of subjects in the dasotraline group that discontinue early and Δ is the shift parameter. By varying Δ, the potential impact of the imputations for subjects with missing data on the final estimate will be assessed. Shift values of .05 (treated subjects have 5% of the change from baseline SKAMP-CS as assumed in the primary methodology) through 1 (treated subjects have 100% of the change from baseline SKAMP-CS as assumed via the primary methodology) will be applied at increments of .05 and reported. The primary analysis will be rerun for all values of Δ and the resulting treatment difference, 95% CI and p-value for each Δ will be reported; the wider the range of values that result in no change in interpretation, the more robust the analysis results may be considered to be.

7.1.2 Multicenter Studies

This study will have up to 5 different clinical sites enrolling and treating subjects. Each site is expected to have a minimum of 12 subjects. For all efficacy analyses where investigative site is an explanatory effect and in by-site subgroup analyses, pooling of sites should not be necessary and is not planned.

7.1.3 Assessment Time Windows

Data will be summarized based on the recorded visit; no visit windowing will be conducted. Visits 4 (Day 1) and 5 (Day 15) must be performed as scheduled based on the protocol, allowing for consistent and reliable efficacy measurements.

7.2 Efficacy Measurements

7.2.1 Swanson, Kotin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale

The SKAMP rating scale is a 13-item independent observer rating of subject impairment (7-point scale) of analog classroom-observed behaviors during the laboratory classroom assessments. Items 1-4 represent an indication of subject attention, items 5-8 are an indication of deportment, items 9-11 assess quality of work, and items 12-13 assess subject compliance with teacher and classroom rules. The specific items associated with these subscales are detailed in Appendix 14.3. In this study, the change from baseline at Day 15 in mean total score of all SKAMP items (or SKAMP-CS) is defined as the primary efficacy parameter. The mean SKAMP-CS on Day 15, the SKAMP-CS at each of the post-dose assessment times on Day 15, the change from baseline at Day 15 in SKAMP-CS at each of the post-dose assessment times, the change from baseline

at Day 15 in mean SKAMP-Attention subscale scores (items 1-4), the SKAMP-Attention subscale scores at each of the post-dose assessment times on Day 15, the change from baseline at Day 15 in SKAMP-Attention subscale scores at each of the post-dose assessment times, the change from baseline at Day 15 in mean SKAMP-Deportment subscale scores (items 5-8), the SKAMP-Deportment subscale scores at each of the post-dose assessment times on Day 15, and the change from baseline at Day 15 in SKAMP-Deportment subscale scores at each of the post-dose assessment times are secondary outcome measures. Higher SKAMP-CS scores signify greater behavioral impairment. Therefore, decreases in SKAMP-CS scores over time will indicate improvement in behavior while increases in SKAMP-CS scores over time will indicate worsening of behavior.

The SKAMP rating scale will be collected during each of 7 class sessions at Visits 4 (Day 1) and 5 (Day 15), occurring at 8:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, and 8:00 pm of the laboratory classroom days. Three practice classroom sessions for the laboratory classroom day will be conducted at Visit 2.

Missing or invalid data for individual questions will be handled by rules specific to the validated SKAMP scale as described in Section 7.1.1.1.

7.2.2 Permanent Product Measurement of Performance (PERMP)

The PERMP is a 5 page math test consisting of 80 problems per page (total of 400 problems). Both attempted problems and correct problems will be assessed. Subjects are to complete as many problems as possible in 10 minutes. The appropriate math level for each subject is determined based on results of a math pretest administered at screening (Visit 2). Performance is measured by the number of math problems attempted (PERMP-A) and the number of math problems correctly completed (PERMP-C). Like the SKAMP, the PERMP will be administered as a practice at Visit 2 and as the final tests at Visits 4 (Day 1) and 5 (Day 15), during each of 7 class sessions occurring at 8:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, and 8:00 pm of the laboratory classroom days. In this study, the change from baseline at Day 15 in PERMP-A and PERMP-C scores at each of the post-dose assessment times and the PERMP-A and PERMP-C scores at each of the post-dose assessment times on Day 15 are defined as secondary efficacy measures. Higher PERMP scores signify higher performance and less severe ADHD symptoms. Therefore, increases in PERMP scores over time will indicate improvement of symptoms, while decreases in PERMP scores over time will indicate worsening of symptoms.

No imputation for missing PERMP values will be performed.

7.3 Eligibility Criteria and ADHD Symptom Control Assessments

7.3.1 Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL)

The K-SADS-PL is used at screening to confirm the diagnosis of ADHD.

The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to Diagnostic and Statistical Manual for Mental Disorders Fourth Edition; Text Revision (DSM-IV-TR) criteria. The K-SADS-PL covers a broad spectrum of most child psychiatric diagnoses, with the exception of pervasive development disorders and personality disorders. The K-SADS-PL includes questions about school performance and other issues relevant to children and adolescents. There is a base instrument (82 items) and 5 required diagnostic supplements which are completed depending on the results of the base screening: (1) Affective Disorders; (2) Psychotic Disorders; (3) Anxiety Disorders; (4) Behavioral Disorders; (5) Substance Abuse and Other Disorders.

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

The ADHD-RS-IV HV is used to assess clinical worsening on Day -1.

The ADHD-RS-IV HV was developed to measure the behaviors of children with ADHD. The ADHD-RS-IV HV is a validated scale that consists of 18 items designed to reflect current symptomatology of ADHD based on Diagnostic and Statistical Manual for Mental Disorders Fourth Edition; Text Revision (DSM-IV-TR) criteria and is also consistent with DSM-5 criteria. Each item is scored from a range of zero (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from zero to 54. Higher ADHD-RS-IV HV total scores signify greater severity in ADHD symptoms.

The following ADHD-RS-IV HV scores will be assessed:

- ADHD-RS Total score (all items).
- ADHD-RS Hyperactivity/Impulsivity subscale score (even number items 2 through 18).
- ADHD-RS Inattentiveness subscale score (odd number items 1 through 17).

No imputation for missing ADHD-RS data will be performed. Descriptive statistics for the ADHD-RS-IV HV scores will be presented for each time point and data will also be presented in a listing.

7.4 Efficacy Outcomes

7.4.1 Primary Efficacy Outcome

The primary efficacy outcome is the change from baseline (Visit 4) at Day 15 (Visit 5) in ADHD symptoms as measured by mean SKAMP-CS obtained from an average of the 7 assessments collected across the 12 hour classroom day (12 to 24 hours post-dose).

7.4.2 Secondary Efficacy Outcomes

Secondary efficacy outcomes include:

- Mean SKAMP-Combined score from the 7 assessments collected across the 12-hour classroom day (12 to 24 hours post-dose) on Day 15
- SKAMP-Combined score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15
- Change from baseline at Day 15 in SKAMP-Combined score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day
- Change from baseline at Day 15 in mean SKAMP-Attention subscale score obtained from the 7 assessments collected across the 12-hour classroom day (12 to 24 hours post-dose)
- SKAMP-Attention subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15
- Change from baseline at Day 15 in SKAMP-Attention subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day
- Change from baseline at Day 15 in mean SKAMP-Deportment subscale score obtained from the 7 assessments collected across the 12-hour classroom day (12 to 24 hours post-dose)
- SKAMP-Deportment subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15
- Change from baseline at Day 15 in SKAMP-Deportment subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day

- Change from baseline at Day 15 in Permanent Product Measure of Performance (PERMP)-Attempted and Correct Problems scores at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day

- PERMP-Attempted and Correct Problems scores at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15

7.5 Analysis Methods

7.5.1 Primary Efficacy Analyses

The primary efficacy analysis will be performed on the ITT population. The primary efficacy outcome is the change from baseline (Visit 4) at Day 15 (Visit 5) in ADHD symptoms as measured by mean SKAMP-CS obtained from an average of the 7 assessments collected across the 12 hour classroom day (12 to 24 hours post-dose).

The key elements of the primary efficacy analysis are as follows:

Data: Change from baseline at Day 15 of mean SKAMP-CS measured on the laboratory classroom days, Visits 4 (baseline) and 5 (Day 15). This will be measured by taking the mean across all 7 assessment time points (8:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, and 8:00 pm) both at baseline and at Day 15. The mean SKAMP-CS will not be rounded prior to analysis. Missing individual item data will first be imputed as described in Section 7.1.1.1 before taking the mean across all assessment time points.

Model: ANCOVA

Fixed effects: The following fixed effects are planned:

- Treatment

- Mean SKAMP-CS at baseline (Visit 4)

- Site

The null hypothesis:

H_0: Change from baseline at Day 15 of the mean SKAMP-CS over all time points from 8:00 am to 8:00 pm on the laboratory classroom days are the same for dasotraline 4 mg/day and placebo

will be tested against the 2-sided alternative hypothesis:

H_1: Change from baseline at Day 15 of the mean SKAMP-CS over all time points from 8:00 am to 8:00 pm on the laboratory classroom days are not the same for dasotraline 4 mg/day and placebo.

The average treatment difference over all post-dose time points will be estimated using LS means from the ANCOVA. The treatment comparison will be conducted as a 2-sided test at the 5% level of significance. The standard error and 95% confidence interval for the treatment difference as well as the treatment effect size will be provided. Effect size will be calculated as the LS mean treatment difference divided by the observed pooled standard deviation.

The primary efficacy analysis will also be repeated for the per protocol (PP) population.

7.5.2 Secondary Efficacy Analyses

The secondary efficacy outcomes include:

- Mean SKAMP-Combined score from the 7 assessments collected across the 12-hour classroom day (12 to 24 hours post-dose) on Day 15
- SKAMP-Combined score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15
- Change from baseline at Day 15 in SKAMP-Combined score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day
- Change from baseline at Day 15 in mean SKAMP-Attention subscale score obtained from the 7 assessments collected across the 12-hour classroom day (12 to 24 hours post-dose)
- SKAMP-Attention subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15
- Change from baseline at Day 15 in SKAMP-Attention subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day
- Change from baseline at Day 15 in mean SKAMP-Deportment subscale score obtained from the 7 assessments collected across the 12-hour classroom day (12 to 24 hours post-dose)

- SKAMP-Deportment subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15

- Change from baseline at Day 15 in SKAMP-Deportment subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day

- Change from baseline at Day 15 in Permanent Product Measure of Performance (PERMP)-Attempted and Correct Problems scores at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day

- PERMP-Attempted and Correct Problems scores at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours post-dose) during the classroom day on Day 15

Descriptive statistics for the SKAMP-CS, SKAMP-Attention subscale scores, SKAMP-Deportment subscale scores, PERMP-A and PERMP-C scores will be calculated for the change from baseline (Visit 4) at Day 15 (Visit 5), average across all time points and for each time point individually for the laboratory classroom day on Day 15, and will be presented for each treatment as well for the differences between the treatments (dasotraline 4 mg/day vs. placebo) based on the ITT population.

In addition, the secondary SKAMP and PERMP efficacy variables will be analyzed based on the same ANCOVA model as described above for the ITT population.

The observed means, LS means and associated standard error bars will be plotted over time for SKAMP-CS and the PERMP scores for the laboratory classroom day at Baseline (Visit 4) and Day 15 (Visit 5) by treatment group. Change from baseline SKAMP-CS, change from baseline SKAMP subscale scores, and change from baseline PERMP scores will be plotted over time at Day 15 (Visit 5) by treatment group. Change from baseline SKAMP-CS will also be plotted over time at Day 15 (Visit 5) by subgroup (age, gender, race).

7.5.3 Examination of Subgroups

The primary efficacy analyses will be repeated on the ITT population based on the following subgroups:

- Gender (Male and Female)

- Race (White, Black or African American, and Other)

- Age (6-9 years and 10-12 years)

8. SAFETY EVALUATION

All safety analyses will be performed on the safety population, which includes subjects who had been treated with dasotraline 6 mg/day under the first version of the protocol. All subjects who were randomized and received at least 1 dose of study medication will be assessed for safety. Safety will be monitored by physical and neurological examinations, vital signs, AEs assessed at each visit, electrocardiography, and clinical laboratory tests. In addition, the C-SSRS will be administered at Screening (Visit 1) and all subsequently scheduled visits to assess emergent suicidal thoughts or behaviors.

8.1 Overview of Safety Analysis Issues

Missing end dates for AEs will not be imputed. If end date information is not available, it will be assumed that the finding or event is ongoing.

Missing AE start dates will be imputed based on the following rules:

- If only the year is known, the date will be set to 01 January of that year. If the year is the same as the year of the first dose of study medication, the date will be set to the date of the first dose of study medication.

- If the year and day are known, the date will be set to January of that year. If the year and day is the same as the year and day of the first dose of study medication, the date will be set to the date of the first dose of study medication.

- If the year and month are known, the date will be set to first day of the month. If the year and month are the same as the year and month of the first dose of study medication, the date will be set to the date of the first dose of study medication.

- If the start date is completely missing, it will be set to the date of the first dose of study medication.

8.2 Overview of Safety Analysis Methods

Safety data will be analyzed descriptively using the safety population described in Section 4.2. Unless specified, all safety summaries will be presented by descriptive statistics, such as number of subjects (n) and percentage for categorical variables and number of subjects (n), mean, standard deviation, median, minimum, and maximum for continuous variables.

8.3 Extent of Exposure

The length of exposure (in days) of study medication will be calculated based on the dates of first and last dosing of study medication (last dosing date - first dosing date + 1). Length of exposure will be summarized by dose (4 mg/day and 6 mg/day) and treatment group on the safety population as continuous values.

For subjects lost to follow-up, no imputation of the length of exposure will be conducted. For subjects who discontinue the study early but return for a follow-up visit, the follow-up data will be used to impute the length of exposure.

8.4 Adverse Events

All AEs will be coded using MedDRA Version 19.0. An AE is any untoward medical occurrence:

- that occurred before, on or after the first dose of study medication,
- with a missing start date and a stop date before, on or after the first dose of study medication, or
- with both a missing start and stop date.

Untoward medical occurrences that occur between the time of informed consent/assent and first study drug administration are pre-treatment events. Those that occur after first administration of study drug are considered AEs. Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed

above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

An AE is considered treatment emergent if it started during or after administration of the first dose of study medication. In addition, medical history events that worsen in severity after the start of dosing will be considered treatment-emergent adverse events (TEAEs). If a subject discontinues early from the study and has an AE after his/her last dosing date, the AE will be deemed as treatment emergent if it occurs ≤72 hours after the last dose and not as treatment emergent if it occurs >72 hours after the last dose of study medication. AEs with partial start dates will be imputed as outlined in Section 8.1 and assigned to the associated treatment period.

Summary Tabulations

An overview of the frequency, i.e., the number and percentage of subjects and events with at least one of the following AEs, will be presented by treatment group (placebo, dasotraline 4 mg/day, dasotraline 6 mg/day, and combined dasotraline [4 mg/day + 6 mg/day]):

- All TEAEs
- SAEs
- TEAEs leading to discontinuation
- Severe TEAEs
- TEAEs related to study medication
- Severe TEAEs
- SAEs related to study medication
- AEs leading to death

System Organ Class and Preferred Term Tabulations

The frequency of subjects reporting TEAEs, along with the frequency of events, will be summarized within each system organ class (SOC) and preferred term (PT) by treatment group. The SOC terms and PTs will be presented in decreasing order of the total number of subjects in the combined dasotraline group (4 mg/day and 6 mg/day)

(frequency) who experienced each AE. System organ class terms and PTs with the same frequency will be presented alphabetically.

Each subject will be counted only once within each SOC and within each PT. If a single subject experienced the same AE more than once within a treatment period, the subject will be counted once per SOC and PT for that AE. For subjects that experienced AEs with multiple severities, the AE with the highest known severity within each SOC and PT will be counted. Adverse events with unassigned/unknown severity will be categorized as severe.

For summaries by relationship to the study medication, AEs will be grouped as “related” or “not related.” AEs assessed as “possible,” “probable,” or “definite,” will be grouped as “related.” If a subject reports more than one AE within the same treatment regimen, SOC and PT, and any are related, it will be summarized as related. AEs whose relationship to treatment is assessed as “not related” or “unlikely” will be grouped as “not related.” Events with unassigned/unknown relationship to study medication will be considered related to study medication.

The frequency of subjects reporting the following AEs, along with the frequency of events, will be summarized and presented by treatment group and MedDRA SOC and PT for the Safety population:

- All TEAEs (including number of events and subject incidence)
- SAEs
- Non-SAEs
- TEAEs leading to discontinuation
- TEAEs by maximum severity (mild, moderate, severe)
- TEAEs by relationship to the study treatment (related, or not related)
- SAEs by relationship to the study treatment
- AEs leading to death

By-Subject Listings

By-subject listings including relevant information (i.e. treatment, age, sex, race, duration of AE, severity, relationship, outcome, action taken, etc.) will be presented for:

- All AEs
- SAEs
- AEs leading to death
- AEs leading to discontinuation (per the case report form)

The onset of AEs will be calculated relative to the first dose of study medication. The duration of AEs in days will be calculated as the difference between the onset and resolution dates of the AE. If the AE is ongoing at the end of the study, or the resolution date is unknown, the duration will be presented as 'Unknown'.

8.5 Adverse Events of Special Concern

Adverse events of special concern for this study are defined as neuropsychiatric and mania related AEs such as ideas of reference; illogical thinking; illusion; childhood psychosis; abnormal behaviour; psychotic disorder; hallucination; hallucination, auditory; hallucination, gustatory; hallucination, olfactory; hallucination, tactile; hallucination, visual; hallucinations, mixed; hypnagogic hallucination; hypnopompic hallucination; somatic hallucination; hallucination, synaesthetic; formication; paranoia; catatonia; delusion; delusional perception; somatic delusion; suspiciousness; tangentiality; thinking abnormal; thought blocking; thought insertion; thought withdrawal; substance-induced psychotic disorder; acute psychosis; delusion of grandeur; delusion of reference; delusion of replacement; derailment; echolalia; echopraxia; erotomanic delusion; jealous delusion; loose associations; magical thinking; persecutory delusion; psychotic behavior; brief psychotic disorder with marked stressors; thought broadcasting; reactive psychosis; impaired reasoning; disorganised speech; mixed delusion; intrusive thoughts; transient psychosis; brief psychotic disorder without marked stressors; mania; hypomania; and substance-induced mood disorder. AEs of special concern will be summarized by PT and treatment group.

8.6 Clinical Laboratory Evaluations

The following laboratory tests will be performed at Screening (Visit 1) and EOS (Visit 6):

- Clinical Chemistry: Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO3), 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

- Hematology: Hemoglobin, Hematocrit, Platelet Count, RBC Count, WBC - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

- Urinalysis: Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

Summary statistics for these laboratory panels (clinical chemistry, hematology and urinalysis) will be provided by treatment group and visit. Laboratory data will also be summarized in shift tables presenting summary statistics of raw data and change from baseline values (means, standard deviations, medians, ranges). All clinical laboratory assessments will be listed for each panel.

In addition, the incidence of markedly abnormal post-baseline laboratory values (MAPLV) will be presented to examine the frequency and percentage of subjects that have values that are potentially clinically significant (PCS). These criteria are outlined in Appendix 14.4.

8.7 Physical and Neurological Examinations

A full physical examination will be performed at Screening (Visit 1) and at the EOS (Visit 6). Body weight will also be measured at Screening (Visit 1), Visit 4, Visit 5, and at the EOS (Visit 6). Height will be measured at Screening (Visit 1).

Clinically significant physical examination findings, as judged by the investigator, at screening will be recorded as medical history and after screening will be recorded as AEs or pre-treatment events depending on the timing in relationship to the first dose of study drug. Abnormal physical exam results will appear in medical history and/or AEs displays and will not be displayed separately.

Neurological examinations will be performed at Screening (Visit 1) and at the EOS (Visit 6) and the parameters will be assessed by the investigator as normal or abnormal. Neurological examination assessments will be summarized using summary statistics for categorical variables (normal/abnormal) by visit. A shift table for baseline condition versus the worst result during the course of the study period (Abnormal > Normal) will be presented by treatment.

8.8 Vital Signs

Vital signs, including respiratory rate; body temperature; supine, standing, and orthostatic blood pressure; supine, standing, and orthostatic heart rate; BMI; and body weight, will be measured at all scheduled in-person study visits (Screening [Visit 1 and Visit 2], Visit 4, Visit 5, and EOS [Visit 6]).

Supine systolic blood pressure, standing systolic blood pressure, orthostatic systolic blood pressure, supine diastolic blood pressure, standing diastolic blood pressure, orthostatic diastolic blood pressure, supine heart rate, standing heart rate, orthostatic heart rate, respiratory rate, body temperature, body weight, and BMI will be summarized descriptively for each visit by treatment group for the absolute value and change from baseline values using descriptive statistics.

In addition, the incidence of sponsor-defined markedly abnormal post-baseline vital sign values will be presented to examine the frequency and percentage of subjects that meet the PCS criteria outlined in Appendix 14.5.

8.9 Electrocardiography (ECG)

A 12-lead ECG will be recorded at Screening (Visit 1) and the EOS visit (Visit 6). All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. The ECG parameters collected will include heart rate, PR interval, RR interval, QT interval, QTc with Bazett correction (QTcB) and QTc with Fridericia correction (QTcF) intervals, QRS duration, and interpretation, including any noted abnormalities. The ECGs will be reviewed and interpreted by the investigator. All data will be assessed for clinical significance.

ECG measurements, overall interpretation, and clinical significance will be summarized descriptively for baseline, each post-dose evaluation, and change from baseline to each post-dose evaluation by treatment group. QT interval, QTcB, and QTcF will also be summarized by < 460 msec, >= 460 msec, < 500 msec, and >= 500 msec, as well as change from baseline < 30 msec, >= 30 msec, < 60 msec, and >= 60 msec, by visit, treatment and age group (6-9 years, 10-13 years).

In addition, the incidence of sponsor-defined markedly abnormal post-baseline ECG values will be presented to examine the frequency and percentage of subjects that meet the PCS criteria outlined in Appendix 14.6.

8.10 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a brief investigator-administered questionnaire that provides for the identification, quantification, and standardized assessment of the occurrences and severity of suicidal ideation and behavior. Subjects will be assessed at Screening (Visit 1) using the Children's Baseline/Screening C-SSRS. For all subsequent testing (Visits 2, 4 and 5 and the EOS visit), the Children's Since Last Visit assessment will be utilized.

The frequency of suicidality using the C-SSRS will be summarized for each visit for each of the following outcomes:

- Number of subjects reporting at least one occurrence of suicidal ideation or behavior.
- Number of subjects reporting any type of suicidal behavior.
- Number of subjects reporting any type of suicidal ideation.

9. PHARMACOKINETIC EVALUATION

No pharmacokinetic sampling is planned for this study.

10. OTHER ANALYSES

Data collected for the 6 mg/day dasotraline arm will be used for exploratory analyses. All subjects in the 6 mg/day arm will be analyzed using the same primary and secondary efficacy analysis methods described in Section 7.5 in a separate model from the 4 mg/day arm. They will also be analyzed for safety as described in Section 8, both separately and pooled with the 4 mg/day dasotraline group.

Dose response and tolerability for dasotraline treated subjects will also be analyzed in a weight-based dose-level analysis. Dose per weight (mg/kg) will be calculated for each dasotraline treated subject and then placed into the following groupings:

- 2 equal-sized groups: 2 groups will be formed based on the median number of dasotraline treated subjects. Each group will contain half of the population of dasotraline treated subjects.

- 3 equal-sized groups: 3 groups will be formed based on tertiles of the number of dasotraline treated subjects. Each group will contain a third of the population of dasotraline treated subjects.

- 4 equal-sized groups: 4 groups will be formed based on quartiles of the number of dasotraline treated subjects. Each group will contain a fourth of the population of dasotraline treated subjects.

- 2 equal-ranged groups: 2 groups will be formed based on the ranges of dose per weight (mg/kg) with cutoff points obtained at 2 equally spaced intervals over the range of mg/kg.

- 3 equal-ranged groups: 3 groups will be formed based on the ranges of dose per weight (mg/kg) with cutoff points obtained at 3 equally spaced intervals over the range of mg/kg.

- 4 equal-ranged groups: 4 groups will be formed based on the ranges of dose per weight (mg/kg) with cutoff points obtained at 4 equally spaced intervals over the range of mg/kg.

Each of these groupings will be analyzed using the same primary efficacy analysis method described in Section 7.5.1. In addition, each of these groupings will be analyzed for safety summarized by PT in descending order for each of the following categories: AEs, SAEs, AEs leading to discontinuation, and AEs of special concern.

A Receiver Operating Characteristic (ROC) analysis will also be conducted based on a logistic regression with dose per weight (mg/kg) as the predictor and AE of special concern as the outcome. An ROC curve for the model will be plotted. The predicted probability of having an AE of special concern event will also be plotted as a function of dose per weight (mg/kg).

Any additional analyses performed after finalization of the SAP will be considered exploratory and will be identified as such in the CSR.

11. INTERIM ANALYSES AND DATA MONITORING

No interim analyses are planned for this study. The Data and Safety Monitoring Board (DSMB) will monitor safety throughout the study. The DSMB will be independent of the Sponsor, CRO, and the investigators and will be empowered to recommend stopping the study due to safety concerns. The membership of the DSMB and its mandate will be described in a separate DSMB charter.

12. CHANGES TO STUDY CONDUCT OR ANALYSES PLANNED IN THE PROTOCOL

12.1 Changes in the Conduct of the Study

No changes are planned as of the date of the SAP.

12.2 Changes in the Analysis Planned in the Protocol

No changes are planned as of the date of the SAP.

13. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583.

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4. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.

14. APPENDICES

14.1 Schedule of Events

	Screening				Double-blind Period		End of Study
	Clinic Visit	Telephone Contact	Practice Laboratory Classroom Session	Telephone Contact	First Laboratory Classroom Day	Second Laboratory Classroom Day	-
	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6
Procedures	Day -35 to -10	Day -9 to -8	Day -7	Day -1	Day 1	Day 15	Day 21[a] (± 2)
Obtain informed consent	X						
Obtain informed assent	X						
Inclusion/Exclusion criteria	X	X	X	X	X		
Randomization					X		
Dispense study drug					X		
Study drug accountability						X	
Medical History	X						
Psychiatric History	X						
Prior/concomitant medication review	X	X	X	X	X	X	X
K-SADS-PL	X						
Physical examination	X						X
Neurological examination	X						X
Height	X						
Weight (including body mass index)	X				X	X	X
Vital signs	X		X		X[b]	X[b]	X
Electrocardiogram (ECG)	X						X
Adverse event monitoring[f]						X	X
Columbia Suicide	X		X		X	X	X

	Screening				Double-blind Period		End of Study
	Clinic Visit	Telephone Contact	Practice Laboratory Classroom Session	Telephone Contact	First Laboratory Classroom Day	Second Laboratory Classroom Day	-
	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6
Procedures	Day -35 to -10	Day -9 to -8	Day -7	Day -1	Day 1	Day 15	Day 21[a] (± 2)
Severity Rating Scale (C-SSRS)							
ADHD-RS-IV HV	X	X[g]		X			X
Classroom Practice Session[c]			X				
SKAMP[d]					X	X	
Math pretest for determination of math level	X						
PERMP[d]					X	X	
Dosing diary distribution/review					X	X	
Hematology/Chemistry	X						X
TSH	X						
Serum β-hCG (in females ≥ 8 years of age)[e]	X						X
Urinalysis	X						X
Urine drug screen	X				X	X	X
Urine β-hCG (in females ≥ 8 years of age)[e]					X	X	

Abbreviations: ADHD-RS-IV HV = ADHD Rating Scale Version IV Home Version (modified for investigator administration), β-hCG = beta-human chorionic gonadotropin, K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime version, PERMP = Permanent Product Measure of Performance, SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale, TSH = thyroid stimulating hormone

[a] Seven (± 2) days after the last dose of study drug, all subjects will return to the clinic and complete assessments.

[b] Heart rate and blood pressure will be measured at approximately the same time on Day 1 and Day 15.

[c] Including practice SKAMP assessments, practice PERMP tests, and other planned activities intended to familiarize subjects with the classroom setting.

[d] Classroom sessions will be started at approximately 8 AM, 10 AM, 12 PM, 2 PM, 4 PM, 6 PM, and 8 PM.

[e] Any positive urine β-hCG test should be confirmed by serum β-hCG.

[f] Pre-treatment events will be collected from the time of informed consent until the first study drug administration.

[g] If the parent/legal guardian cannot be reached, these assessments may be performed on Day -7.

14.2 Sample Laboratory Classroom Day Schedule

Nominal Time	Actual Time	Arrival	PERMP/SKAMP	Meal/snack	Dismissal
	6:30 am	X			
	7:30 am			X	
12 h postdose	8:00 am		X		
	9:45 am			X	
14 h postdose	10:00 am		X		
16 h postdose	12:00 pm		X		
	12:30 pm			X	
18 h postdose	2:00 pm		X		
	2:30 pm			X	
20 h postdose	4:00 pm		X		
22 h postdose	6:00 pm		X		
	6:30 pm			X	
24 h postdose	8:00 pm		X		
	8:45 pm				X

14.3 SKAMP Rating Scale and Subscales

Subscale	Item
Attention	1. Getting started on assignments for classroom periods
	2. Sticking with tasks or activities for the allotted time
	3. Attending to an activity or a discussion of the class
	4. Stopping and making transition to the next period
Deportment	5. Interacting with other children (e.g., other students)
	6. Interacting with adults (e.g., teacher or aide)
	7. Remaining quiet according to classroom rules
	8. Staying seated according to classroom rules
Quality of Work	9. Completing assigned work
	10. Performing work accurately
	11. Being careful and neat while writing or drawing
Compliance	12. Complying with teacher's usual requests or directions
	13. Following the rules established for the classroom

14.4 Laboratory Criteria for Markedly Abnormal Values

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
Haematocrit (fraction, %)	≤ 30, ≥ 50	1 / %	≤ 30, ≥ 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
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
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
Urinalysis			
RBC (hpf)	> 15	N/A	> 15
WBC (hpf)	> 15	N/A	> 15

14.5 Vital Signs Criteria for Markedly Abnormal Values

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.

14.6 12-Lead ECG Criteria for Markedly Abnormal Values

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
	12 to <16	--	> 110
	≥16	--	> 120