Dasotraline (SEP-225289)

Clinical Study Protocol SEP360-311

Dasotraline (2mg) in Children Aged 6 to 12 Years with Attention-Deficit Hyperactivity Disorder (ADHD): A Randomized, Multicenter, Double-blind, Placebo-controlled, Parallel-group Study of Efficacy and Safety in a Laboratory Classroom Setting

IND No. 071283

Version 3.00

Incorporates Amendment 2.00

19 November 2017

SUNOVION PHARMACEUTICALS INC.
84 Waterford Drive
Marlborough, MA 01752, USA
(508) 481-6700

RESTRICTED DISTRIBUTION OF PROTOCOLS

This document contains information confidential and/or of proprietary interest to Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc. (including their predecessors, subsidiaries or affiliates). The information cannot be disclosed to any third party or used for any purpose other than the purpose for which it is being submitted without the prior written consent of the appropriate Sumitomo Dainippon Pharma Company.

This information is being provided to you for the purpose of conducting a clinical study for Sunovion Pharmaceuticals Inc. You may disclose the contents of this protocol to the study personnel under your supervision and to your Institutional Review Board or Independent Ethics Committee for the above purpose. You may not disclose the contents of this protocol to any other parties, unless such disclosure is required by government regulations or laws, without the prior written permission of Sunovion Pharmaceuticals Inc.

Any data gathered during the conduct of this protocol and supplemental information (e.g., a protocol amendment) that may be added to this document is also proprietary to Sunovion Pharmaceuticals Inc, and should be handled consistently with that stated above. This document contains information confidential and/or of proprietary interest to Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc. (including their predecessors, subsidiaries or affiliates). The information cannot be disclosed to any third party or used for any purpose other than the purpose for which it is being submitted without the prior written consent of the appropriate Sumitomo Dainippon Pharma Company.

EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician		
Medical Monitor		
SAE/Pregnancy Reporting		

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: Dasotraline (SEP-225289)

Title of Study: Dasotraline (2mg) in Children Aged 6 to 12 Years with Attention-Deficit Hyperactivity Disorder (ADHD): A Randomized, Multicenter, Double-blind, Placebo-controlled, Parallel-group Study of Efficacy and Safety in a Laboratory Classroom Setting

Proposed Indication: Attention-Deficit Hyperactivity Disorder (ADHD)

Study Centers: Approximately 5 centers in North America

Planned Study Period: 4-6 months

Study Objectives:

Primary: To evaluate the efficacy of dasotraline 2 mg/day compared to placebo on attention-deficit hyperactivity disorder (ADHD) symptoms in children (6 – 12 years of age), who weigh ≤ 30 kg, in a laboratory classroom setting.

Secondary:

- To evaluate the efficacy of dasotraline 2 mg/day compared to placebo on ADHD symptoms throughout the day (12 to 24 hours post-dose) in children in a laboratory classroom setting.
- To evaluate the safety and tolerability of dasotraline 2 mg/day using physical examinations, 12-lead electrocardiograms (ECG), vital signs, adverse event (AE) reports, clinical laboratory results, and the Columbia – Suicide Severity Rating Scale (C-SSRS) Children's Assessment.

Study Design: 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 be comprised of 3 periods: Screening (up to 35 days) including a 3 - 5 day ADHD medication washout prior to Day -1, if necessary; Double-blind randomized treatment with either dasotraline (2 mg/day) or placebo for 14 days; and a final safety evaluation 7 days after last dose. Prior to the start of treatment (Day 1) and following the conclusion of the double-blind period (Day 15), subjects will undergo a full-day laboratory classroom evaluation in cohorts of up to 18 subjects. Each laboratory classroom day will include seven 30-minute simulated classroom sessions where trained observers will assess subjects using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) 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. Seven (± 2) days after the last dose of study drug, subjects will return to the clinic and complete safety assessments.

The primary efficacy endpoint will be the change from baseline to Day 15 in ADHD symptoms as measured by the mean SKAMP-Combined score obtained from an average of the 7 SKAMP assessments collected across the 12-hour classroom day. The SKAMP is a validated 13-item rating scale that assesses manifestations of ADHD in a classroom setting through a combined score and 2 subscale scores; deportment items (interacting with other children, interacting with adults, remaining quiet, staying seated, complying with the teacher's directions, and following the classroom rules) and attention items (getting started, sticking with tasks, attending to an activity, making activity transitions, completing assigned tasks, performing work accurately, and being neat and careful while writing or drawing). 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 the math pretest administered at screening.

Safety and tolerability will be monitored throughout the study by physical and neurological examinations, 12-lead ECG, vital signs, AEs, clinical laboratory evaluations (hematology, chemistry, and urinalysis), and the C-SSRS. A Data and Safety Monitoring Board (DSMB) will review safety and tolerability data including data on AEs and serious AEs at regular intervals.

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 from the subject and informed consent from at least one of the subject's parents/legal guardians.

Subjects will be confirmed as meeting DSM-5 criteria for a diagnosis of ADHD. Subjects may be either currently untreated or receiving stimulant ADHD medication at Screening. On Day -7 the ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV) will be completed and 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. Any subjects receiving stimulant medication for ADHD will discontinue that ADHD treatment for 3 - 5 days prior to Day -1 in order to ensure that there is at least a 72-hour washout before 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 the presence of clinically significant ADHD symptoms since discontinuation of stimulant medication. Clinically significant is defined as an ADHD-RS-IV HV total score ≥ 26 following a minimum 72-hour washout from any prior ADHD treatment. Subjects who do not demonstrate clinically significant symptoms (i.e., ADHD-RS-IV ≥ 26) on Day -1 will be considered screen failures and will not be eligible for randomization.

Subjects may be rescreened a maximum of 2 times for out of range clinical laboratory results, insufficient medication washout periods, etc.

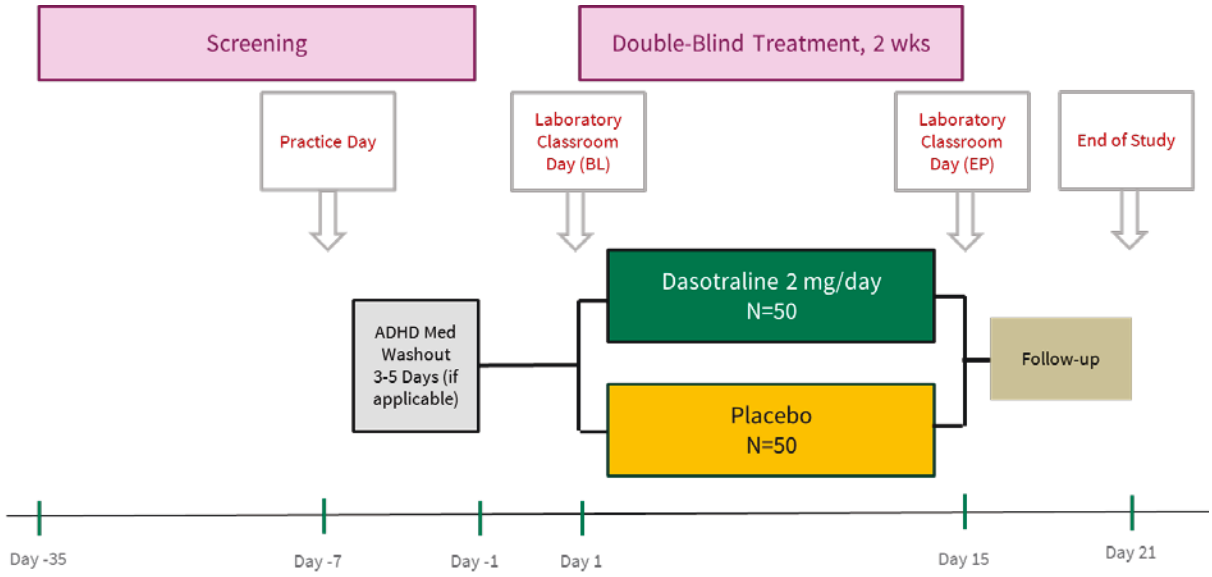
Double-blind Period: On Day 1 subjects will return to the clinic in the morning, and those meeting all inclusion and no exclusion criteria will be randomized (1:1) to receive 2 mg/day dasotraline, or placebo, and will attend classroom sessions in which they will be evaluated for ADHD symptoms using the 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) after the final, 8:00 PM baseline classroom assessment. Subjects will 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 at approximately 8 PM plus or minus 30 minutes, in the clinic after all assessments are completed and before the subject leaves, or at home. On the night (Day 14) before the second classroom day, study drug must be taken at approximately 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 at 6:30 AM 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 and 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. A summary of assessments to be conducted at each visit is presented in Table 2, Schedule of Assessments.

A sample Classroom Day is presented in Table 3.

Study Schematic



Number of Subjects (planned): This study is projected to randomize approximately 100 subjects (50 per treatment group).

Diagnosis and Main Criteria for Subject Inclusion:

1. Male or female subjects between 6 and 12 years of age.
2. Subject weighs ≤ 30 kg at the time of screening.
3. Subjects in general good health are eligible to participate.
4. Subjects must meet Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (inattentive, hyperactive, or combined presentation) at screening, established by a comprehensive psychiatric evaluation that reviews DSM-5 criteria. Diagnosis will be confirmed at screening using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL).
5. Subject is currently either untreated for ADHD or receiving a treatment regimen of a stimulant medication prescribed as monotherapy treatment within the approved labeled dose range for ADHD.
6. Subject, in the opinion of the investigator, is not treatment refractory.
7. For any subject receiving monotherapy stimulant treatment for ADHD, that treatment must be well tolerated and clinically effective. Note: If any doses of ADHD pharmacotherapy were missed during the week prior to Day -7, the subject's eligibility will be discussed with the Medical Monitor.
8. Subject, on Day -1, has evidence of clinically significant ADHD symptoms as measured by an ADHD-RS-IV HV total score ≥ 26. If subject has been receiving stimulant pharmacotherapy for ADHD the ADHD RS-IV should be administered following a minimum 72-hour washout from prior ADHD medication treatment.

Subject Exclusion:

Subjects with any of the following conditions are ineligible for participation in the study:

1. Subject currently has a diagnosis of asthma that has required daily treatment with bronchodilators or nebulizer treatments in the 30 days prior to screening and/or who may require daily treatments with these agents over the course of the trial (intermittent use of bronchodilators is not exclusionary; subjects who have a history of requiring persistent asthma treatment should be discussed with the medical monitor prior to randomization).
2. Subject has a diagnosis of bipolar I or II disorder, major depressive disorder, conduct disorder, obsessive-compulsive disorder, disruptive mood dysregulation disorder (DMDD), intellectual disability, any history of psychosis, autism spectrum disorder, Tourette's Syndrome, or confirmed genetic disorder with cognitive and/or behavioral disturbances; generalized anxiety disorder or panic disorder that has been the primary focus of treatment at any time during the 12 months prior to screening; or that required pharmacotherapy any time during the 6 months prior to the start of screening.
3. Subject has failed 2 adequate courses (dose and duration) of stimulant or non-stimulant treatment for ADHD.
4. Subject is considered treatment refractory by the investigator.
5. Subject shows evidence of any chronic disease of the central nervous system (CNS) such as tumors, inflammation, seizure disorder, vascular disorder, potential CNS related disorders that might occur in childhood.
6. Subjects with a history of persistent neurological symptoms attributable to serious head injury; history of febrile seizure, drug-induced seizure, or alcohol withdrawal seizure.
7. Any use of anticonvulsants for seizure control currently or within the past 2 years.
8. Uncontrolled thyroid disorder indicated by thyroid stimulating hormone (TSH) ≤ 0.8 x the lower limit of normal (LLN) or ≥ 1.25 x the upper limit of normal (ULN) for the reference laboratory.
9. Any history of attempted suicide, clinically significant suicidal ideation, or answers "yes" to "Suicidal Ideation" item 4 or item 5 for any lifetime history on the C-SSRS Children's Lifetime/Recent assessment at screening.
10. Subjects having first-degree relatives (biological parent or sibling) with a history of schizophrenia, schizoaffective disorder, bipolar I disorder, or bipolar II disorder are also ineligible for the study.

Investigational Product, Dosage and Mode of Administration: Each daily dose will be supplied as one 2 mg dasotraline capsule for oral administration.

Duration of Treatment: 2 weeks

Reference Therapy, Dosage and Mode of Administration: Each daily dose will be supplied as one matching placebo capsule for oral administration.

Selected Concomitant Medications: Subject must not have taken any of the following medications: anticonvulsants for seizure control within 2 years prior to screening; antipsychotic medication within 6 months prior to screening; herbal and/or complementary treatments, e.g., St. John's Wort, or antidepressant medications (e.g., bupropion, serotonin norepinephrine reuptake inhibitor [SSRI]/ selective serotonin reuptake inhibitor [SNRI], tricyclic, etc.) within 6 months prior to Day 1, monoamine oxidase (MAO) inhibitors at any time, or non-stimulant product as treatment for ADHD within 4 weeks prior to the start of screening.

Any subjects receiving stimulant medication for ADHD will discontinue that ADHD treatment for

3 - 5 days prior to Day -1 in order to ensure that there is at least a 72-hour washout before the assessment of ADHD symptoms on Day -1. Treatment with any ADHD medication is prohibited during the washout period. In addition, all subjects are required to refrain from other prohibited medications for at least 7 days, unless otherwise specified, prior to the first dose of study drug.

Use of any of the following medications is not permitted during the study from screening through the EOS visit: lithium; alpha-2 adrenergic receptor agonists (including clonidine and guanfacine), modafinil, armodafinil, atomoxetine, or any stimulant class agent (methylphenidate- or amphetamine-based); antidepressant medications (e.g., bupropion, SSRI/SNRI, MAO inhibitor, tricyclic, etc.); anticonvulsant medications (e.g., phenytoin, carbamazepine, lamotrigine, valproic acid, etc.); antipsychotic medications; pseudoephedrine-containing medications; medications with significant effect on blood pressure or heart rate (intermittent use of asthma treatments is permitted but should be discussed with the medical monitor); sleep aids (with the exception of melatonin); diphenhydramine except topical formulations; herbal and/or complementary treatments, e.g., St. John's Wort; or CYP2B6 substrates or inhibitors or inducers of CYP2B6. Subjects who require persistent asthma treatment during the study should be discussed with the medical monitor as they may be required to be discontinued from the study.

Use of any of the following behavioral interventions is not permitted during the study from screening through the EOS visit. This includes: ongoing or newly initiated Cognitive Behavioral Therapy (CBT) for the treatment of ADHD; behavioral therapies, including school based interventions that were initiated less than one month prior to screening; and, behavioral therapy that in the opinion of the investigator would interfere with the subject's ability to participate for the duration of the study.

School based interventions that have been in place for more than one month prior to screening will be allowed.

Note: Unavoidable changes in school-based interventions that occur during study participation will not be exclusionary, but should be documented by the investigator, to the extent possible. Subjects should not be enrolled who, in the judgment of the investigator, are expected to start substantially different or more intensive course of behavioral therapy over the duration of their participation in the study.

Study Endpoints:

Primary Endpoint: Change from baseline at Day 15 in ADHD symptoms as measured by mean SKAMP-Combined score obtained from an average of the 7 assessments collected across the 12-hour classroom day (12 to 24 hours post-dose).

Secondary Endpoints:

- 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 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.
- Change from baseline at Day 15 in mean PERMP-Attempted score obtained from an average of the 7 assessments collected across the 12 hour classroom day (12 to 24 hours post-dose).
- Change from baseline at Day 15 in mean PERMP-Correct score obtained from an average of the 7 assessments collected across the 12 hour classroom day (12 to 24 hours post-dose).
- The incidence of overall AEs, serious AEs (SAEs), and AEs (or SAEs) leading to discontinuations.
- Absolute values and change from baseline in clinical laboratory evaluations (serum chemistry, hematology, and urinalysis).
- Absolute values and changes from baseline in vital signs, body weights, and 12-lead ECGs.
- Frequency and severity of suicidal ideation and suicidal behavior as assessed by the C-SSRS.

Statistical Methods:

Hypotheses:

Let $\mu_{2mg/day}$, and μ_{PBO} represent the changes from baseline at Day 15 in mean SKAMP-Combined score for dasotraline 2 mg/day, and placebo arms, respectively. The following hypothesis will be tested to compare the mean change value between the dasotraline 2 mg/day group and the placebo group from baseline to Day 15:

1. Dasotraline 2 mg/day versus placebo:

H_{01}: $\mu_{2mg/day} = \mu_{PBO}$ versus H_{11}: $\mu_{2mg/day} \neq \mu_{PBO}$

Efficacy Analysis:

An analysis of covariance (ANCOVA) will be applied to evaluate the treatment effect for the primary efficacy endpoint between the dasotraline 2 mg/day and placebo groups for the intent-to-treat (ITT) population. The model will include treatment, mean SKAMP-Combined score at baseline, and site as fixed effects. The primary efficacy analysis will be repeated for the per protocol (PP) population. To explore the robustness of the primary efficacy analysis of change from baseline at Day 15 in ADHD symptoms in mean SKAMP-Combined score, 2 sensitivity analyses will be performed, a placebo-based multiple imputation pattern-mixture model (PMM) and a tipping point analysis using the PMM.

A similar ANCOVA model, as described above, will be used for the secondary efficacy endpoints for the ITT population.

Multiplicity Considerations: There will be no adjustment for multiplicity for the primary efficacy analysis, secondary efficacy analyses, or safety analyses.

Safety Analysis:

All safety analyses will be performed on the safety population. Overall AEs (or SAEs) and AEs (or SAEs) leading to discontinuation will be summarized by system organ class and preferred term by presenting the number and percentage of subjects with each AE. Descriptive statistics also will be provided by visit for observed values and changes from baseline for the following safety variables:

laboratory tests, vital signs, and ECG parameters. Frequency and severity of suicidality, as captured by the C-SSRS, will be summarized by visit.

Sample Size:

A post-hoc ANCOVA-LOCF analysis of data from the SEP360-305 laboratory classroom study was conducted to examine the effect of dasotraline 4 mg/day versus placebo in a subset of pediatric patients with ADHD aged 6-9 years old. This analysis showed an effect size in this subgroup of 0.95 (LS mean difference at Week 2 was 7.2 with a standard error of 2.2). Assuming a smaller effect size for dasotraline 2 mg/day vs. placebo than that of dasotraline 4 mg/day vs. placebo, an effect size of 0.7 was utilized for the sample size calculation.

Therefore, assuming an effect size of 0.7 for dasotraline 2 mg/day compared to placebo on the primary efficacy endpoint of mean SKAMP-Combined score obtained from the average of 7 assessments collected across the 12-hour classroom day, 88 subjects (44 per treatment group) will provide 90% power to detect a treatment effect between dasotraline and placebo at the two-sided alpha level of 0.05, based on the two-sample t-test with equal variance procedure.

The study will target approximately 100 subjects (50 per treatment group) randomized to either placebo or dasotraline 2 mg/day in an attempt to have 88 subjects complete the trial (assuming a 12% overall dropout rate).

Table 2: Schedule of Assessments

	Screening			Double-blind Period		End of Study
	Clinic Visit	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 -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		
Randomization				X		
Dispense study drug				X		
Study drug accountability					X	
Medical History	X					
Psychiatric History	X					
Family Psychiatric History	X					
Prior/concomitant medication review	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 Severity Rating Scale (C-SSRS)	X	X		X	X	X

Table 2: Schedule of Assessments (Continued)

	Screening			Double-blind Period		End of Study
	Clinic Visit	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 -8	Day -7	Day -1	Day 1	Day 15	Day 21[a] (± 2)
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] The ADHD-RS-IV HV may be completed in person or by telephone contact on Day -9, -8, or -7.

Table 3: Sample Laboratory Classroom Day Schedule (Day 15)

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

Abbreviation: h = hour, PERMP = Permanent Product Measure of Performance, SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 4 and Table 5.

Table 4: List of Abbreviations

Abbreviation	Full Form
ADHD	Attention deficit hyperactivity disorder
ADHD-RS-IV	ADHD Rating Scale Version IV
ADHD-RS-IV HV	ADHD Rating Scale Version IV - Home Version (modified for investigator administration)
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical (class)
BMI	Body mass index
CAP	College of American Pathologists
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity of Illness
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTM	Clinical trial material
DAT	Dopamine transporter
DBL	Database lock
DEA	Drug Enforcement Agency
DHPG	3, 4-dihydroxyphenylglycol
DMDD	Disruptive mood dysregulation disorder
DMP	Data Management Plan
DNRI	Dopamine and norepinephrine, reuptake inhibitor
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Disorders Fourth Edition; Text Revision

Table 4: List of Abbreviations (Continued)

Abbreviation	Full Form
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HR	Heart rate
IAF	Informed assent form
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ITT	Intention-to-Treat
IUD	Intrauterine device
IXRS	Interactive response system
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version
LLN	Lower limit of normal
MAO	Monoamine oxidase (inhibitor)
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NET	Norepinephrine transporter
ODD	Oppositional defiant disorder
PD	Protocol deviations
PERMP	Permanent Product Measure of Performance
PMM	Pattern-mixture model
POC	Point of care
PP	Per-Protocol

Table 4: List of Abbreviations (Continued)

Abbreviation	Full Form
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
PVG	Pharmacovigilance
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
QTcB	QTc with Bazett correction
QTcF	QTc with Fridericia correction
RR	Electrocardiographic interval between 2 consecutive R waves
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SOC	System organ class
TSH	Thyroid stimulating hormone
UDS	Urine drug screen
ULN	Upper limit of normal
USP	United States Pharmacopeia
WHO	World Health Organization
WHO-DD	World Health Organization drug dictionary

Table 5: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failure	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled/randomized.
Study Drug (or Study medication)	Term to cover investigational drug, placebo, and/or active control.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into the treatment period of the study and was assigned a randomization number.
Completed Subject	Any subject who participated throughout the duration of the study, up to and including both visits 5 and 6.
Early Termination Subject	Any subject who was successfully screened and randomized into the treatment period of the study, but did not complete the study.
End of Treatment	The day that the subject received the protocol-defined last dose of the study drug.
End of Study	The day that the subject completes the study per the study design.

4. INTRODUCTION

4.1. Background

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent inattention, hyperactivity, and impulsivity that is more severe or frequent when compared to individuals of the same developmental stage. There are a number of characteristics related to cognition that distinguish people with ADHD from people without ADHD including deficits in response inhibition (Aron-2005, Goto-2010, Luna-2004) and reward sensitivity (Passarotti-2011), as well as working memory, attention, planning, and behavioral inhibition (Hervey-2004, Boonstra-2005, Willcutt-2005). ADHD is prevalent in approximately 8% to 10% of school-aged children and approximately 2% to 5% of adults (Ferri-2014). Symptoms experienced in childhood often persist into adolescence and adulthood, although the hyperactivity component tends to diminish over time (Ferri-2014).

The etiology of ADHD is not fully understood, but it is believed that both genetic and non-genetic factors are implicated in the disease. Several factors related to disturbances of neonatal development including premature birth, low birth weight and perinatal complications have been shown to increase the risk of developing ADHD in childhood (Perricone-2013, Botting-1997, Amor-2005).The neurotransmitters dopamine and norepinephrine are proposed to have a critical role in the development of ADHD and thus receptors associated with these are key drug targets (Rader-2009).

Current ADHD pharmacotherapies have effects on central catecholamine neurotransmission. In nonclinical microdialysis studies, ADHD drugs like amphetamine, methylphenidate, and atomoxetine increase dopamine and norepinephrine – either by reuptake inhibition or stimulation of release – especially in the prefrontal cortex. At clinically-efficacious doses, 50% dopamine transporter (DAT) occupancies are reported with methylphenidate in adults with ADHD (Volkow-1998).

Adrenergic signaling in the prefrontal cortex is thought to control attentional processes and thus contribute to working memory and executive functions (Arnsten-2011, Gamo-2011). Consistent with this neuronal circuitry, norepinephrine transporter (NET) inhibition (eg, atomoxetine) alone is sufficient for clinical efficacy in ADHD. The stimulants amphetamine and methylphenidate both increase norepinephrine concentrations centrally, and methylphenidate achieves 50% NET occupancy in human subjects at doses clinically efficacious in ADHD (Hannestad-2010).

Dasotraline (also known as SEP-225289) is a new chemical entity that is thought to produce its therapeutic effects in ADHD by inhibition of the presynaptic DAT and NET, as determined by receptor occupancy and microdialysis studies. Pharmacologically, dasotraline is consistent with dopamine and norepinephrine reuptake inhibitor (DNRI) effects. Dasotraline is a diastereomer of the major metabolite of the selective serotonin reuptake inhibitor sertraline, but is not a metabolite of sertraline, nor is it converted to the desmethylated metabolite of sertraline in vivo. Unlike amphetamines, dasotraline does not increase the release of these monoamines into the extraneuronal space. Dasotraline's pharmacokinetic profile allows plasma concentrations to remain in a therapeutic range over the 24-hour dosing interval at steady state.

As there is a considerable unmet medical need for ADHD medications in children and adolescents that optimize onset and duration of action, Sunovion believes dasotraline, a novel inhibitor of NET and DAT, may be a useful addition to the current treatment armamentarium. Based on the available data dasotraline may provide steady, full-day coverage of DAT and NET inhibition. Dasotraline is being evaluated as a once daily treatment for children, adolescents and adults with ADHD with possible therapeutic coverage across the 24-hour dosing interval.

4.2. Study Conduct Rationale

Dasotraline has been evaluated for the treatment of ADHD in 4 completed placebo controlled studies, 2 in adults and 2 in children 6 -12 years of age. Moreover, an open label de novo study in adults and an open label extension study in children have also been completed. Additional studies on the pharmacokinetics and abuse liability of the compound have also shown the drug to have a tolerable profile.

This will be the third study to assess the efficacy and safety of dasotraline in pediatric subjects with ADHD. The prior 2 studies demonstrated efficacy at 4 mg in comparison to placebo. This study will utilize a simulated classroom setting, identical to the one used in SEP360-305, to evaluate the efficacy and safety of dasotraline 2 mg/day in pediatric subjects with ADHD. In this setting subjects encounter activities and interaction normally found in a typical school day. The laboratory school protocol (Wigal-2006) is a particularly useful method for evaluation of efficacy in subjects with ADHD because it represents a controlled study setting for evaluation and comparison of study treatments.

The present study seeks to evaluate the efficacy and safety of dasotraline 2 mg/day. Data supporting the safety and efficacy of both a 2 mg and a 4 mg dose would afford a range of potential doses (2-4 mg/day) for children, allowing clinicians the flexibility to achieve the optimal benefit/risk for each patient.

Further information on nonclinical and other clinical studies is provided in the Investigator's Brochure.

4.3. Risk-Benefit Assessment

There are two recently completed studies in children with ADHD that report on the efficacy and tolerability of dasotraline (SEP360-202 and SEP360-305), both of which demonstrated statistically significant improvement compared to placebo at the 4 mg/day dose. A third study, SEP360-310, has been completed but the analyses are not yet finalized.

SEP360-202

SEP360-202 evaluated the efficacy and safety of 2 doses of dasotraline (2 mg/day and 4 mg/day) in pediatric subjects with ADHD. In this 6-week double-blind, placebo controlled trial, dasotraline (4 mg/day) was superior to placebo, and well tolerated.

In SEP360-202, overall, 54.1% of subjects experienced at least 1 Treatment Emergent Adverse Event (TEAE) during the study, 38.6% experienced a TEAE that was considered by the Investigator to be related to study drug, and 6.7% experienced a TEAE that led to discontinuation of study drug. Subjects in the dasotraline 4 mg/day group experienced more

TEAEs, more related TEAEs, and more TEAEs that led to a discontinuation than the dasotraline 2 mg/day group and the placebo group, and the placebo group experienced the least in each of these categories. No subjects experienced an SAE and there were no deaths during the study.

SEP360-305

SEP360-305 evaluated the efficacy and safety of dasotraline (4 mg/day) to placebo, in pediatrics with ADHD in a classroom laboratory setting over 2 weeks. The dasotraline (4 mg/day) dose demonstrated statistically superior efficacy when compared to placebo, and was well tolerated.

In SEP360-305, TEAEs were more common in patients taking dasotraline compared with those taking placebo (data from the discontinued 6 mg arm of this trial are included here for safety consideration). TEAEs were generally mild or moderate in severity. Four patients receiving dasotraline experienced severe TEAEs: 4 mg/day: 1 case of insomnia and 1 case of decreased appetite; 6 mg/day: 2 cases of insomnia. No serious AEs occurred in patients treated with dasotraline. TEAEs associated with discontinuation were hallucinations (2 cases in the 6 mg/day group, 1 case in the 4 mg/day group), insomnia (1 case in the 4 mg/day group), decreased appetite (1 case in the 6 mg/day group), and rash (1 case in the 4 mg/day group).

Moreover, there have been three studies of dasotraline efficacy and tolerability in adults with ADHD including one long term de novo trial for safety; SEP360-201, SEP360-301, and SEP360-304 respectively.

SEP360-201

The first study (SEP360-201), a randomized, double-blind, parallel-group, outpatient study at 30 sites, evaluated the efficacy and safety of dasotraline in adults with ADHD using 2 doses (4 mg/day or 8 mg/day) versus placebo over a 4-week treatment period. In this study, clinically meaningful treatment effects were observed for both dasotraline 4 mg/day and 8 mg/day compared to placebo. For the primary efficacy endpoint, change from baseline in ADHD Rating Scale Version IV (ADHD RS-IV) with adult prompts total score at week 4, statistical significance was achieved for dasotraline 8 mg/day compared to placebo (adjusted $p = 0.019$) with a strong trend for dasotraline 4 mg/day (adjusted $p = 0.076$). Efficacy with both doses was observed for the secondary endpoint Clinical Global Impression–Severity of Illness (CGI-S; 4 mg group $p = 0.021$; 8 mg group $p = 0.013$). A dose response relationship was observed supporting pharmacological activity in ADHD. Decreases in 3,4-dihydroxyphenylglycol (DHPG) concentrations indicated the presence of central NET inhibition. Adverse events (AEs) were consistent with dasotraline pharmacology, ie, insomnia, decreased appetite, dry mouth, and headache. Worsening of insomnia associated with dasotraline was characterized by AEs, and shifts in Insomnia Severity Index (ISI) total score, particularly with dasotraline 8 mg/day. AEs, particularly insomnia, were the most frequent reason for discontinuation of dasotraline 8 mg/day. Decreases in mean body weight were generally greater for dasotraline 8 mg/day than 4 mg/day. Increases in mean supine and standing heart rate observed during treatment and follow-up were generally higher on dasotraline 8 mg/day than 4 mg/day

SEP360-301

The second adult study (SEP360-301) evaluated the efficacy and safety of dasotraline (4 mg/day and 6 mg/day) and although the doses were found safe, and the 6 mg arm showed numerically greater improvement over placebo, neither dose was statistically significantly different than placebo.

SEP360-304

The third study (SEP360-304) showed that dasotraline, flexibly dosed from 4 mg/day to 8 mg/day, appeared to be safe, well tolerated, and effective in adults for the long term treatment of ADHD. Given the long half-life of dasotraline, dosing increments at a frequency of no more than every 2 weeks may improve overall tolerability.

The pharmacokinetics and abuse potential for dasotraline have been assessed in several studies.

One study was completed that evaluated the safety, tolerability, pharmacokinetic, and pharmacodynamic properties of dasotraline in pediatric (6 – 12 years) and adolescent (13 - 17 years) subjects with ADHD. In this multicenter, open-label study 105 subjects were assigned to single oral doses of dasotraline 1 - 16 mg in a dose-escalating manner. Dasotraline was characterized by slow absorption (median t_{max} was 9.6 to 12 hours) and elimination (median $t_{½}$ was 56 to 84 hours) in both pediatric and adolescent subjects. The change in C_{max} with dose was slightly greater than dose proportional. Increase in overall exposure (AUC) with dose was greater than dose proportional. Apparent oral clearance was highest in the lowest dose group relative to the higher dose groups. No deaths, serious adverse events (SAE), or discontinuations because of an adverse event (AE) were reported in this study. The most frequently reported AE by investigators were tachycardia (25 subjects; 23.8%) and electrocardiogram QT prolonged (5 subjects; 4.8%), nearly all of which were considered related to study drug and mild in severity. Tachycardia AEs were reported in both age groups and in every dose cohort. Most events of tachycardia were reported on the day of study drug administration. No subjects experienced QT prolongations > 500 msec. Based on the centrally read electrocardiogram (ECGs) in the study, no clinically significant trends were identified within the ECG results. Blood pressure increased, blood pressure systolic increased, blood pressure orthostatic abnormal, and orthostatic hypotension AEs were reported in 1 subject each. Overall, after dosing, 90 subjects (85.7%) met predefined criteria for orthostatic tachycardia and 40 (38.1%) met predefined criteria for orthostatic hypotension.

Two studies have been completed to support dasotraline as a compound with minimal abuse potential. The first study (SEP360-201), a randomized, double-blind, parallel-group, outpatient study at 30 sites, evaluated the efficacy and safety of dasotraline in adults with ADHD using 2 doses (4 mg/day or 8 mg/day) versus placebo over a 4-week treatment period. No signs or symptoms of withdrawal upon discontinuation of dasotraline were observed for either dose. In addition, there was no evidence of drug liking or deterioration of psychiatric symptoms associated with either dose of dasotraline. No misuse or diversion of dasotraline was detected through the abuse potential monitoring plan. A second study evaluated dasotraline's abuse liability and was conducted in recreational stimulant users; results indicated that dasotraline has

low abuse liability (Koblan-2016). All doses of dasotraline (8, 16, 36 mg) demonstrated significantly lower drug liking scores than methylphenidate (40, 80 mg) and were no greater than placebo.

Four previous clinical studies in healthy adult subjects using single doses ranging from 0.2 mg to 36 mg and doses of 1 mg/day to 3 mg/day for durations up of 21 days, and another study in adult subjects with major depressive disorder (MDD) using doses of 0.5 mg/day and 2 mg/day for up to 8 weeks (56 days) also have been completed. In these clinical studies, dasotraline was generally safe and well tolerated at the doses studied and there was no evidence of abuse or diversion and no symptoms of withdrawal.

4.4. Hypothesis

This study is designed to test the superiority of dasotraline 2 mg/day against placebo based on Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP)-Combined score in pediatric subjects aged 6-12 years with ADHD who weigh ≤ 30 kg.

5. STUDY OBJECTIVES

5.1. Primary Objectives

The primary objective is to evaluate the efficacy of dasotraline 2 mg/day compared to placebo on attention-deficit hyperactivity disorder (ADHD) symptoms in children (6 - 12 years of age) in a laboratory classroom setting as measured by the change form baseline at Day 15 in SKAMP Combined Score.

5.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of dasotraline compared to placebo on ADHD symptoms throughout the day (12 to 24 hours postdose) in children in a laboratory classroom setting as measured by sub scores of the SKAMP and PERMP.
- 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.

6. STUDY ENDPOINTS

6.1. Primary Endpoints

The primary endpoint is change from baseline at Day 15 in ADHD symptoms as measured by mean SKAMP-Combined score obtained from an average of the 7 assessments collected across the 12-hour classroom day (12 to 24 hours postdose).

6.2. Secondary Endpoints

The secondary endpoints are:

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

- Change from baseline at Day 15 in mean PERMP-Attempted score obtained from an average of the 7 assessments collected across the 12-hour classroom day (12 to 24 hours postdose).
- Change from baseline at Day 15 in mean PERMP-Correct score obtained from an average of the 7 assessments collected across the 12-hour classroom day (12 to 24 hours postdose).
- The incidence of overall AEs, serious AEs (SAEs), and AEs (or SAEs) leading to discontinuations
- Absolute values and change from baseline in clinical laboratory evaluations (serum chemistry, hematology, and urinalysis)
- Absolute values and changes from baseline in vital signs, body weights, and 12-lead ECGs
- Frequency and severity of suicidal ideation and suicidal behavior as assessed by the C-SSRS

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study, in pediatric subjects with ADHD in a laboratory classroom setting. The study will target 100 subjects (50 per treatment group) to complete the study. The study will be comprised of 3 periods: Period 1: screening (up to 35 days) including a 3 - 5 day ADHD medication washout, if necessary, prior to Day -1; Period 2: double-blind randomized treatment with either dasotraline (2 mg/day) or placebo for 14 days; and 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 up 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 SKAMP 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 to endpoint change in the SKAMP-Combined score.

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. A Data and Safety Monitoring Board (DSMB) will review safety and clinical outcome data including data on AEs and serious AEs at regular intervals.

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 from the subject and informed consent from at least one of the subject's parents/legal guardians.

Subjects will be confirmed as meeting DSM-5 criteria for a diagnosis of ADHD. Subjects may be currently untreated for ADHD or receiving a treatment regimen of stimulant medication for ADHD at Screening. On Day -7 the ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV) will be completed and 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. Any subjects receiving stimulant medication for ADHD will discontinue that ADHD treatment for 3 - 5 days prior to Day -1 in order to ensure that there is at least a 72-hour washout before 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 the presence of clinically significant ADHD symptoms. Clinically significant is defined as an ADHD-RS-IV HV total score ≥ 26. Subjects who do not demonstrate clinically significant symptoms on Day -1 will be considered screen failures and will not be eligible for randomization.

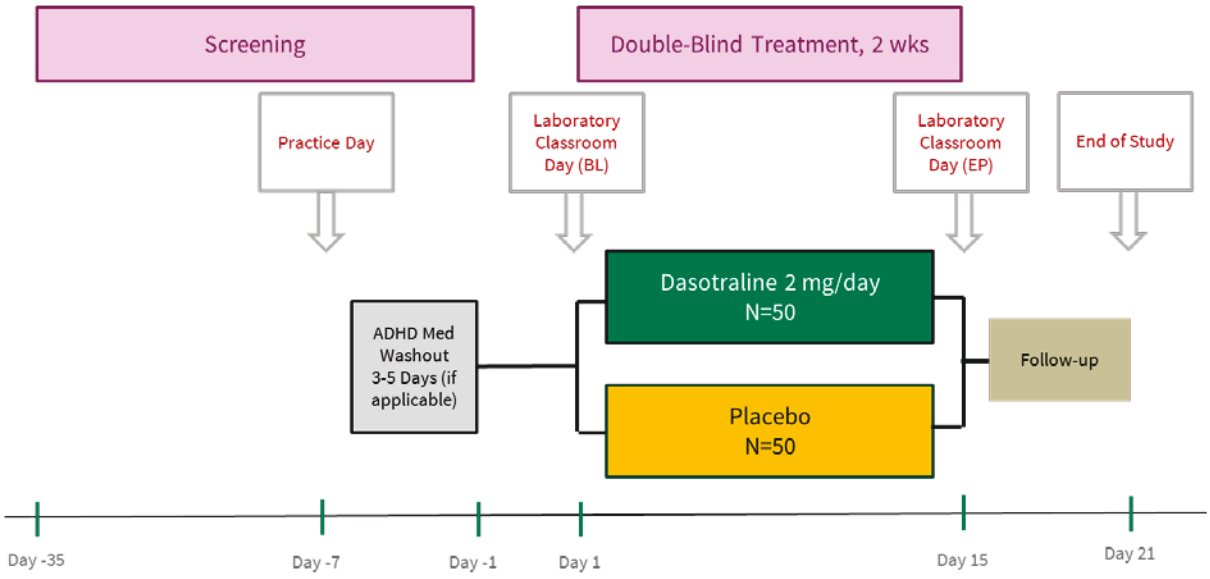
Subjects may be rescreened a maximum of 2 times for out of range clinical laboratory results, insufficient medication washout periods, etc.

Double-blind Period: On Day 1 subjects will return to the clinic in the morning, and those meeting all inclusion and no exclusion criteria will be randomized (1:1) to receive 2 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) after the final, 8:00 PM baseline classroom assessment. Subjects will 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 after all assessments are completed and before the subject leaves, or at home. On the night (Day 14) before the second classroom day, study drug must be taken at approximately 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 at 6:30 AM 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 and 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 Table 2, Schedule of Assessments, and Section 11, Study 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 Table 3 with additional details provided in the Laboratory Classroom Manual.

Figure 1: Study Schematic



7.2. Treatment Assignment and Blinding

7.2.1. Treatment Assignment

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

- 2 mg/day dasotraline (N = 50 subjects)
- Placebo (N = 50 subjects)

An Interactive Response System (IXRS) will be used to manage randomization on Day 1 and, if necessary, for emergency unblinding (see Section 7.2.3) 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.

7.2.2. Blinding

This is a double-blind study. All study drug capsules (both dasotraline and placebo) are identical in color, shape, size, and packaging in order to maintain the blind.

Subjects, Sponsor personnel, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories will remain blind to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods; (1) randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of Data and Safety Monitoring Board (DSMB) members involved in regular review of safety data, and Clinical Trial Materials Management personnel, (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, and appearance.

7.2.3. Emergency Unblinding Procedures

The IXRS will be used, if necessary, for emergency unblinding of treatment assignment during the study. The blinded dose information is to be broken only in an emergency when knowledge of such treatment may have an impact on further treatment decisions or aid in the emergency treatment of the subject. Any subject for whom the blind is broken is to be discontinued from receiving any additional study drug and should undergo early termination procedures as described in Section 14.

7.3. Rationale

7.3.1. Rationale for the Study Design

The current study is a randomized, double-blind, placebo-controlled, parallel-group, laboratory classroom study in pediatric subjects with ADHD weighing ≤ 30 kg. This study was designed to evaluate the efficacy and duration of effect of dasotraline (2 mg/day) compared with placebo over an entire day in a simulated classroom setting. The laboratory school protocol is a particularly useful method for evaluation of efficacy in subjects with ADHD because it

represents a controlled study setting for evaluation and comparison of study treatments and is designed to mimic a typical school day.

7.3.2. Rationale for the Dosages

The dosage of 2 mg/day of dasotraline was selected to evaluate dasotraline safety, tolerability, and efficacy within the dose range being evaluated in the ongoing studies in pediatric subjects with ADHD.

A dasotraline 2 mg/day dose is expected to produce mg/kg exposures in pediatric subjects weighing ≤ 30 kg similar to those demonstrated to be effective in both children and adults with ADHD. In prior studies it was noted that AEs appear to be dose related. Therefore, 2 mg in smaller children may be efficacious and better tolerated.

7.3.3. Rationale for the 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); diagnosis will be confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL). Subjects are required to weigh ≤ 30 kg since a 2 mg/day dose in such a group is expected to have mg/kg exposures similar to those demonstrated to be effective in children and adults.

7.3.4. Rationale for the Endpoints

The primary efficacy measure (mean SKAMP-Combined Score) is a widely accepted efficacy endpoint intended to assess functional impairment related to ADHD and has been used in many laboratory classroom studies in children (Childress-2015, Wigal-2014).

7.4. Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study prior to study completion, the following study design and conduct elements are implemented; (i) use of clinical sites with a good track record of having performed this type of study, (ii) training provided to the clinical sites on the importance of the informed consent/assent process and ensuring subjects and their parent/guardian understand the commitment they are making, including the intent to complete the trial, and (iii) monitoring data collection for adherence during the study.

8. SELECTION OF SUBJECTS

Subjects may be rescreened a maximum of 2 times for out of range clinical laboratory results, insufficient medication washout periods, etc.

8.1. Subject Inclusion Criteria

The subjects who fulfill the following criteria will be included in the study.

1. Subject is 6 - 12 years old, inclusive at screening and randomization.
2. Subject weighs ≤ 30 kg at the time of screening.
3. At least one of the subject's parents/legal guardians must give written informed consent, including privacy authorization, prior to study participation. The subject will provide informed assent prior to study participation.
4. Subject meets Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (inattentive, hyperactive, or combined presentation) at screening established by a comprehensive psychiatric evaluation that reviews DSM-5 criteria and confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) at screening.
5. Subject is currently either untreated for ADHD or receiving a treatment regimen of a stimulant medication prescribed as monotherapy (i.e., methylphenidate, mixed amphetamine salts, lisdexamphetamine, or dextroamphetamine) within the approved labeled dose range for ADHD.
6. In the opinion of the investigator, the subject is not treatment refractory.
7. Any subject not receiving ADHD medication at screening must display clinically significant ADHD symptoms, as measured by an ADHD-RS-IV score ≥ 26 at screening and Day -7.
8. For any subject receiving monotherapy stimulant treatment for ADHD, that treatment must be well tolerated and clinically effective based on clinical assessment and informant interview, as well as, review of available medical records. Note: The ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV) will be administered at Screening by the investigator to inform clinical evaluation.
9. Subject is male or a non-pregnant, non-lactating female.
10. Subject, if female, must not be pregnant or breastfeeding, and if ≥ 8 years of age must have a negative serum pregnancy test at screening.
11. Female subjects of childbearing potential and male subjects with female partners of childbearing potential must practice true abstinence (consistent with lifestyle) and must agree to remain abstinent or agree to use an effective and medically acceptable form of birth control, from the time of informed consent/assent to at least 14 days after the last dose of the study drug has been taken. See Section 10.5 for information on acceptable methods of birth control.

12. Subject must be in general good health (defined as the absence of any clinically relevant abnormalities as determined by the investigator) based on screening physical and neurological examinations, medical history, and clinical laboratory values (hematology, chemistry, and urinalysis). Note: If any of the hematology, chemistry, or urinalysis results are not within the laboratory's reference range, then the subject can be included only if the investigator determines the deviations to be not clinically relevant.
13. Subject is within the 3rd to 97th percentile for gender specific weight-for-age from the Centers for Disease Control and Prevention (CDC) growth charts. See Sections 24, and 25, Appendix V and VI for growth charts.
14. Subject must report a history of being able to swallow capsules.
15. Subject and subject's parent/legal guardian must be able to fully comprehend the informed consent/assent forms, understand and be willing and able to comply with all study procedures and visit schedule, and be able to communicate satisfactorily with the investigator and study coordinator.
16. Subject, on Day -1, has evidence of clinically significant ADHD symptoms as measured by an ADHD-RS-IV HV total score ≥ 26. If subject has been receiving stimulant pharmacotherapy for ADHD the ADHD-RS-IV should be administered following a minimum 72-hour washout from prior ADHD medication treatment.

8.2. Subject Exclusion Criteria

The subjects who meet any of the following criteria will be excluded from the study

1. Subject or parent/legal guardian has commitments during the study that would interfere with attending study visits.
2. Subject is currently being treated for ADHD with a non-stimulant product, or has been treated with a non-stimulant product in the 4 weeks prior to the start of screening.
3. Subject has failed 2 adequate courses (dose and duration) of stimulant or non-stimulant treatment for ADHD.
4. Subject is considered treatment refractory, as judged by the investigator.
5. Subject currently has a diagnosis of asthma that has required daily treatment with bronchodilators or nebulizer treatments in the 30 days prior to screening and/or who may require daily treatments with these agents over the course of the trial. Intermittent use of bronchodilators is not exclusionary. Subjects who have a history of requiring persistent asthma treatment should be discussed with the medical monitor prior to randomization.
6. Subject has any clinically significant unstable medical abnormality, chronic disease, or a history of a clinically significant abnormality of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems, or a disorder or history of a condition (eg, malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion. Note: Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. In cases in which the impact of the condition upon risk to the subject or study results is unclear, the medical monitor should be consulted. Any subject with a known

cardiovascular disease or condition (even if controlled) must be discussed with the medical monitor during screening.

7. Subject has a history or presence of abnormal ECGs, which in the investigator's opinion is clinically significant. Screening site ECGs will be centrally over-read, and eligibility will be determined by the investigator based on the results of the over-read report.
8. Subject has any diagnosis of bipolar I or II disorder, major depressive disorder, conduct disorder, obsessive-compulsive disorder, any history of psychosis, autism spectrum disorder, disruptive mood dysregulation disorder (DMDD), intellectual disability, Tourette's Syndrome, confirmed genetic disorder with cognitive and/or behavioral disturbances. Note: Subjects with oppositional defiant disorder (ODD) are permitted to enroll in the study as long as ODD is not the primary focus of treatment.
9. Subject has a first-degree relative (biological parent or sibling) with a history of schizophrenia, schizoaffective disorder, bipolar I disorder, or bipolar II disorder.
10. Subject has generalized anxiety disorder or panic disorder that has been the primary focus of treatment at any time during the 12 months prior to screening or that has required pharmacotherapy any time during the 6 months prior to screening.
11. Subject has evidence of any chronic disease of the central nervous system (CNS) such as tumors, inflammation, seizure disorder, vascular disorder, potential CNS related disorders that might occur in childhood (eg, Duchenne Muscular dystrophy, myasthenia gravis, or other neurologic or serious neuromuscular disorders).
12. Subjects with a history of persistent neurological symptoms attributable to serious head injury.
13. History of febrile seizure, drug-induced seizure, or alcohol withdrawal seizure is exclusionary.
14. Subjects taking anticonvulsants for seizure control currently or within the past 2 years are not eligible for study participation.
15. Subject has uncontrolled thyroid disorder as evidenced by thyroid stimulating hormone (TSH) $\leq$ 0.8 x the lower limit of normal (LLN) or $\geq$ 1.25 x the upper limit of normal (ULN) for the reference laboratory.
16. Subject answers "yes" to "Suicidal Ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) for any lifetime history on the C-SSRS Children's Lifetime/Recent assessment at screening.
17. Subject has any history of attempted suicide or clinically significant suicidal ideation, in the opinion of the investigator.
18. Subject has a history of severe allergies to more than 1 class of medication or multiple adverse drug reactions or has a history of allergic reaction or has a known or suspected sensitivity to any substance that is contained in the study drug formulations.
19. Subject has history of intolerance (safety) or lack of efficacy to stimulants.
20. Subject has taken any antipsychotic medication within 6 months prior to screening.

21. Subject has taken any herbal and/or complementary treatments, eg, St. John's Wort, within 6 months prior to Day 1.
22. Subject has taken any antidepressant medication (eg, bupropion, selective serotonin reuptake inhibitor [SSRI]/ serotonin norepinephrine reuptake inhibitor [SNRI], tricyclic, etc) within 6 months prior to Day 1.
23. Subject has ever taken any monoamine oxidase [MAO] inhibitor at any time.
24. Subject is currently undergoing ongoing or newly initiated Cognitive Behavioral Therapy (CBT) for the treatment of ADHD; behavioral therapies, including school based interventions that were initiated less than one month prior to screening; or, behavioral therapy that in the opinion of the investigator would interfere with the subject's ability to participate for the duration of the study. School based interventions that have been in place for more than one month prior to screening will be allowed. Note: Unavoidable changes in school-based interventions that occur during study participation will not be exclusionary, but should be documented by the investigator, to the extent possible. Subjects should not be enrolled who, in the judgment of the investigator, are expected to start substantially different or more intensive course of behavioral therapy over the duration of their participation in the study.
25. Subject or subject's family anticipates a move outside the geographic range of investigative site during the study period, or plans extended travel inconsistent with the recommended visit interval during study duration.
26. Subject has history of, or current, malignancy other than non-melanomatous skin cancer.
27. Subject has history of positive test for Hepatitis B surface antigen or Hepatitis C antibody.
28. Subject is known to have tested positive for human immunodeficiency virus (HIV).
29. Subject has participated in a classroom study within 6 months prior to the start of screening or has participated in any other clinical study with an investigational drug/product within 90 days prior to the start of screening or is currently participating in another clinical trial.
30. Subject shows evidence of substance or alcohol use or is currently using tobacco or other nicotine-containing products, or has a positive urine drug screen (UDS) at screening. Note: Subjects with a positive UDS may be allowed to continue in the study, provided that the investigator determines that the positive test is as a result of taking medications as prescribed after consultation with the medical monitor.
31. Subject is taking any disallowed medications for chronic treatment.
32. Subject has previously been enrolled in a clinical trial of dasotraline (SEP-225289).
33. Subject's parent/legal guardian is an investigational site staff member or the relative of an investigational site staff member.
34. Subject is, in the opinion of the investigator, unsuitable in any other way to participate in this study.

35. Subject's sibling or family member living in the same household is participating in the same laboratory classroom cohort for this study.
36. Subject is unable to perform at the basic level of the standardized math test as defined in the laboratory classroom manual.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

The study medication is described in Table 6.

Table 6: Investigational Product

Attribute	Investigational Product	
Product name	Dasotraline 2 mg	Matching Placebo
Dosage form	Capsules	Capsules
Unit dose	One capsule	One capsule
Route of administration	Oral	Oral
Physical description	Swedish orange, size #4	Swedish orange, size #4

In addition to dasotraline, the active ingredient, each capsule contains: Mannitol United States Pharmacopeia (USP), Sodium Starch Glycolate NF, Talc USP, and Magnesium Stearate NF.

The matching placebo capsule is identical to dasotraline in color, shape, size, and packaging and contains all ingredients, except the active dasotraline.

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

Study drug will be provided in 1 week blister cards containing 10 capsules of dasotraline 2 mg or placebo capsules (7 days + 3 extra days).

9.2.2. Labeling Description

All packaging for the study drug will be labeled with:

- Protocol number
- Sponsor's name and address
- Content (eg number of capsules)
- Investigational New Drug statement
- Instructions for use and storage
- Blank space for subject identifiers
- Batch number
- Unique medication number

9.3. Study Drug Storage

All study medication should be stored at USP Controlled Room Temperature: 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). The subject's parent(s)/legal guardian(s) will be instructed to store the study medication at room temperature.

In addition, the subject's parent(s)/legal guardian(s) will be instructed to store the study medication in a location where it cannot be inadvertently accessed and consumed by the subject and to remove all other ADHD treatments from the subject's access.

9.4. Dispensing of Study Drug

An Interactive Response System (IXRS) will be used to manage subject screening and enrollment. The IXRS is an integrated web-based subject and drug management system. Specific User Manuals will be supplied.

Study medication blister cards will be assigned by the IXRS based on the treatment schedule. The IXRS will generate instructions on which medication number to assign to a subject. Appropriate guidelines should be followed in proper dispensation to the study participant. Each subject will be dispensed two 1-week blister cards on Day 1. Proper accountability records must be maintained and accurately document all drug dispensing activities.

Under supervision from the subject's parent/legal guardian, subjects will self-administer the study drug on an outpatient basis (see Section 10.1). The daily dosage (one capsule) will be clearly labeled on the study drug blister card.

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by subjects. If the study is stopped for any reason or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/ clinical research organization (CRO).

Upon receipt of clinical trial material (CTM) the Principal Investigator, or designee, will inventory the supplies and verify receipt of supplies. The site will send an Acknowledgement of Receipt to Sunovion Pharmaceuticals, or designee, confirming date of receipt, inventory, and condition of CTM received.

The Investigator, or designee, agrees to collect and document all used and unused study medication from study subjects/parents/legal guardians at appropriate study visits.

Study drug will not be dispensed to any person who is not a study subject under this protocol.

On Day 1 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 the parent/legal guardian will bring the dosing diary to the visit. Only the date and time of the Day 14 dose will be entered into the database.

9.6. Study Drug Handling and Disposal

A drug inventory record will be supplied by the Sponsor/CRO. The Investigator or designee on an ongoing basis must maintain a drug inventory record of supplied, received, dispensed, and returned study drug. The Investigator or designee is required to return all unused supplies of study drug as well as empty packaging from used study drug to the Sponsor or designee as instructed. The Investigator or designee is required to maintain copies of medication shipping receipts, drug accountability records, and records of return or final disposal of the study drug in accordance with local regulatory requirements.

10. TREATMENT OF SUBJECTS

10.1. Study Medication

As described in Section 7.2.1, subjects will be randomized to 1 of 2 treatments (2 mg/day dasotraline or placebo).

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 should be taken at approximately the same time each evening. The first dose of study drug may be administered in the clinic, at approximately 8 PM plus or minus 30 minutes, after all assessments are completed, before the subject leaves, or at home. On Day 14, the night before the second classroom day, study drug must be taken at approximately 8 PM plus or minus 30 minutes. All study medication doses will consist of 1 capsule per day taken by mouth.

Subjects may take study drug with or without food.

Study drug capsules should not be opened or tampered with in any way; the active ingredient is an ocular irritant.

10.2. Treatment Compliance

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.

The Investigator will record the dose of the study drug and the dates of the initial and final administration for each dose.

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. Evidence of noncompliance must be immediately reported to the Medical Monitor. Potential noncompliance will be discussed with subjects and their parent(s)/legal guardian(s), and at the investigator's discretion may result in termination of the subject from the study. All subjects and their parent(s)/legal guardian(s) will be reminded of the importance of strict compliance with taking study drug for the effectiveness of treatment and for the successful outcome of the study.

10.3. Concomitant Medications and Therapies

The following information on all medication administered between signed consent/assent and the EOS visit or at discontinuation will be recorded on the CRF: Medication name, dose, frequency, route, start date, stop date, and indication.

All medications will be coded using World Health Organization drug dictionary (WHO-DD). Information on the format and version of the coding dictionary will be provided in the Data Management Plan (DMP).

Collection of prior medications is described in Section 11.1.

10.3.1. Prohibited Medications

Subject must not have taken any of the following medications within the timeframe listed:

- Anticonvulsants for seizure control within 2 years prior to screening
- Antipsychotic medication within 6 months prior to screening
- Herbal or complementary treatments, eg, St. John's Wort, within 6 months prior to Day 1
- Any antidepressant medication (eg, bupropion, SSRI/ SNRI, tricyclic, etc) within 6 months prior to Day 1
- MAO inhibitor at any time
- Non-stimulant product as treatment for ADHD within 4 weeks prior to the start of screening.

Any subjects receiving stimulant medication for ADHD will discontinue that ADHD treatment for 3 - 5 days prior to Day -1 in order to ensure that there is at least a 72-hour washout before the assessment of ADHD symptoms on Day -1. Treatment with any ADHD medication is prohibited during the washout period. In addition, all subjects are required to refrain from other prohibited medications for at least 7 days, unless otherwise specified, prior to the first dose of study drug.

Use of any of the following medications is not permitted during the study from screening through the EOS visit:

- Lithium (any lithium preparation or formulation)
- Alpha-2 adrenergic receptor agonists (including clonidine and guanfacine), modafinil, armodafinil, atomoxetine, or any non-stimulant class agent
- Antidepressant medications (eg, bupropion, SSRI/SNRI, MAO inhibitor, tricyclic, etc)
- Anticonvulsant medications (eg, phenytoin, carbamazepine, lamotrigine, valproic acid, etc) and antipsychotic medications
- Pseudoephedrine-containing medications
- Medications with significant effect on blood pressure or heart rate. Intermittent use of asthma treatments is permitted but should be discussed with the medical monitor.
- Sleep aids with the exception of melatonin
- Diphenhydramine except topical formulations
- Herbal or complementary treatments, eg, St. John's Wort
- CYP2B6 substrates or inhibitors or inducers of CYP2B6 (see Section 23, Appendix IV).

10.4. Restrictions

Subject is currently undergoing ongoing or newly initiated Cognitive Behavioral Therapy (CBT) for the treatment of ADHD; behavioral therapies, including school based interventions that were initiated less than one month prior to screening; or, behavioral therapy that in the opinion of the investigator would interfere with the subject's ability to participate for the duration of the study.

School based interventions that have been in place for more than one month prior to screening will be allowed.

Note: Unavoidable changes in school-based interventions that occur during study participation will not be exclusionary, but should be documented by the investigator, to the extent possible. Subjects should not be enrolled who, in the judgment of the investigator, are expected to start substantially different or more intensive course of behavioral therapy over the duration of their participation in the study.

10.5. Contraception Requirements

Female Subjects

A female subject is eligible to enter and participate in the study if she is of:

a. Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is premenarchal, surgically sterile, etc.).
b. Child-bearing potential (all females ≥ 8 years of age), has a negative pregnancy test at screening and agrees to satisfy one of the following requirements:

   - Practice true abstinence (consistent with lifestyle) from signing informed consent/assent to at least 14 days after the last dose of study drug; or,
   - Use of medically effective method of birth control from signing informed consent/assent to at least 14 days after the last dose of study drug, which include: prescription hormonal contraceptives (oral, patch, vaginal ring, implant, or injection), diaphragm with spermicide, intrauterine device (IUD), condom with spermicide, surgical sterilization.

Male Subjects

Male subject must be willing to remain sexually abstinent (consistent with lifestyle) or with female partner(s) of childbearing potential must ensure that their partner(s) uses the methods of birth control as outlined for female subjects above.

10.6. Guidance for Overdose

There is no overdose experience with dasotraline in humans. Signs and symptoms of overdose in nonclinical studies were consistent with exaggerated pharmacology and included hyperactivity, stereotypy, aggressiveness, and reduced food intake and body weight loss.

Activated charcoal may be of value if administered very soon after a dasotraline overdose (i.e., during the absorption process).

10.7. Cautions

Dasotraline is an ocular irritant. Therefore appropriate precautions should be taken to avoid ocular exposure to the contents of the dasotraline capsules.

10.8. Dietary Guidelines

Study drug may be taken without regard for food.

During the practice laboratory classroom session and the laboratory classroom days, meals and snacks will be provided as described in the Laboratory Classroom Manual.

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 1. A summary of assessments to be conducted at each visit is presented in Table 2, Schedule of Assessments.

Training, as appropriate, will be provided for study site staff administering each of the effectiveness and safety assessments.

11.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics include date of birth, sex, ethnicity, race, and medical history. For medical, psychiatric, and family psychiatric histories, only relevant/significant history and recurrence of any condition will be collected. All medications taken during the 30 days before signed consent/assent will be recorded; data collected will be the same as for concomitant medications (see Section 10.3). Weight, height, and BMI collection are described in Section 11.4.5. Physical and neurological examinations are described in Section 11.4.4.

11.2. Eligibility Assessments

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

The K-SADS-PL will be 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.

The K-SADS-PL takes about 45-90 minutes to administer.

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

The ADHD-RS-IV HV will be used to assess the presence of clinically significant ADHD symptoms 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. The 18 items may be grouped into 2 subscales: hyperactivity/impulsivity (even number items 2 through 18) and inattentiveness (odd number items 1 through 17). The ADHD-RS-IV HV will be administered to the caregiver

by a qualified rater at the site. The same study site rater should perform all ADHD-RS-IV HV assessments for a given subject whenever possible.

11.3. Efficacy Assessments

Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Scale

The SKAMP is a validated 13-item rating scale that assesses manifestations of ADHD in a classroom setting through a combined score and 2 subscale scores; deportment items (interacting with other children, interacting with adults, remaining quiet, staying seated, complying with the teacher's directions, and following the classroom rules) and attention items (getting started, sticking with tasks, attending to an activity, making activity transitions, completing assigned tasks, performing work accurately, and being neat and careful while writing or drawing).

Permanent Product Measure 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.

11.4. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct.

11.4.1. Adverse Events

Adverse events will be collected for each subject. Parents/guardians should be queried in a non-leading manner, without specific prompting (if the child has complained about changes in health and how the child has been feeling). Subjects should also be queried in a non-leading manner, without specific prompting (e.g., "How have you been feeling? Have you felt different?). See Section 12, Safety Reporting

AEs and SAEs will be monitored throughout the study at all visits starting after the first dose of study drug.

Untoward medical occurrences that occur prior to the first dose of study drug will be collected as pre-treatment events.

11.4.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 22, Appendix III.

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed centrally. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical

laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

Any POC (point of care) kits that are performed on site by study personnel rather than in a lab- must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.4.3. Vital Signs

Respiratory rate and oral body temperature will be measured following 5 minutes of supine rest.

An appropriately sized blood pressure cuff should be used based on the subject's size. Blood pressure and pulse rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and pulse rate will be taken again after the subject has been standing for ≥ 5 minutes. The same arm should be used during each assessment of blood pressure and pulse rate throughout the study. If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and pulse rate should be collected at that time in the manner described above. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

11.4.4. Physical and Neurological Examinations

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.

Neurological examination parameters will be assessed by the investigator as normal or abnormal.

11.4.5. Weight and Body Mass Index

Body weight while wearing street clothes and without shoes will be recorded in kilograms (kg). Height without shoes will be recorded in centimeters (cm). Body mass index will be calculated by the electronic data capture (EDC) system using height measured at screening and weight from the appropriate visit.

11.4.6. ECGs

Centrally-read ECG: All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. Refer to Section 20, Appendix I for additional information.

Standard 12 lead ECG will record heart rate (HR), PR interval, RR interval, QT interval, QTc with Bazett correction (QTcB) and QTc with Fridericia correction (QTcF) intervals, and QRS duration.

11.4.7. Safety Scales

Columbia Suicide Severity Rating Scale (C-SSRS) Children's Assessment

The C-SSRS (Posner-2007) is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the site.

This study will utilize 2 versions of the C-SSRS. At the screening visit, the lifetime/recent version will be completed; for all subsequent visits the "Since Last Visit" version of the C-SSRS will be administered.

Subjects who have significant findings for suicidal ideation upon completion of the C-SSRS at any time during the study must be referred to the investigator for follow-up evaluation.

11.5. Study Visits and Assessments

11.5.1. Screening

Subjects may be rescreened a maximum of 2 times for out of range clinical laboratory results, insufficient medication washout periods, etc.

11.5.1.1. Visit 1 (Day -35 to -8)

Subjects will be evaluated at this visit to determine their eligibility to enroll in the study. The following study-related procedures will be performed:

- Obtain informed consent/assent
- Review inclusion/exclusion criteria
- Collect medical, psychiatric, and family psychiatric histories
- Record prior and concomitant medications
- Perform physical and neurological examinations
- Measure height and weight, record BMI
- Collect vital signs
- Perform ECG
- Administer K-SADS-PL, C-SSRS lifetime/recent version, ADHD-RS-IV HV, math pretest for placement level
- Collect samples for clinical laboratories (hematology, serum chemistry, TSH, urinalysis), UDS, serum pregnancy test for females ≥ 8 years of age

11.5.1.2. Visit 2 (Day -7): Practice Laboratory Classroom Session

At this visit the following study-related procedures will be performed:

- Review inclusion/exclusion criteria
- ADHD-RS-IV HV. Note: The ADHD-RS-IV HV may be completed in person or by telephone contact on Day -9, -8, or -7.

- Record prior and concomitant medications
- Collect vital signs
- Administer C-SSRS since last visit version
- Conduct Laboratory Practice Classroom Session. Details are provided in the Laboratory Classroom Manual.

11.5.1.3. Visit 3 (Day -1): Telephone Contact

The parent/legal guardian of the subject will be contacted by telephone to determine the subject's continued eligibility for the study. The following study-related procedures will be performed:

- Review inclusion/exclusion criteria
- Record prior and concomitant medications
- Administer ADHD-RS-IV HV

If a subject does not demonstrate an ADHD-RS-IV HV total score ≥ 26 then he or she is not eligible to continue in the study.

11.5.2. Double-blind Period

11.5.2.1. Visit 4 (Day 1): First Laboratory Classroom Day

At this visit the subject should arrive at the clinic by 6:30 AM and the following study-related procedures will be performed:

- Record prior and concomitant medications
- Review inclusion/exclusion criteria
- Measure weight, record BMI
- Collect vital signs once.
- Administer C-SSRS since last visit version
- Collect samples for UDS, urine pregnancy test for females ≥ 8 years of age
- Randomize to treatment
- Dispense study drug
- Provide dosing diary
- Conduct 7 classroom sessions according to a Laboratory Classroom Manual common to all investigational sites.

Subjects will begin taking double-blind study drug on the evening of Day 1 at approximately 8 PM plus or minus 30 minutes. The first dose of study drug may be administered in the clinic, after all assessments are completed, or at home.

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.

11.5.2.2. Visit 5 (Day 15): Second Laboratory Classroom Day

At this visit the subject should arrive at the clinic by 6:30 AM and the following study-related procedures will be performed:

- Perform study drug accountability
- Collect dosing diary
- Record prior and concomitant medications
- Record AEs
- Measure weight, record BMI
- Collect vital signs once. For each subject the time should be the same as on Day 1.
- Administer C-SSRS since last visit version
- Collect samples for UDS, urine pregnancy test for females ≥ 8 years of age
- Conduct 7 classroom sessions according to the Laboratory Classroom Manual.

11.5.3. Visit 6 (Day 21 ± 2): End of Study

Final safety assessments will be completed at this visit. The following study-related procedures will be performed:

- Record prior and concomitant medications
- Perform physical and neurological examinations
- Measure weight, record BMI
- Collect vital signs
- Perform ECG
- Record AEs
- Administer C-SSRS since last visit version, ADHD-RS-IV HV
- Collect samples for clinical laboratories (hematology, serum chemistry, urinalysis), UDS, serum pregnancy test for females ≥ 8 years of age

All subjects including those who discontinue study drug prior to completion will be asked to return 7 (± 2) days after the last dose of study drug and complete the EOS visit.

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.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from after first administration of study drug to the last study visit.

Lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way.

New signs and symptoms of underlying disease, or signs and symptoms of emerging disease must be recorded as AEs.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

12.1.2. Serious Adverse Events

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.

The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.3); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as

"serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (e.g., elective surgery) that was scheduled before the study entry, i.e., before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

Clinically significant abnormal objective findings (e.g., clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (e.g., viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (e.g., clinically significant elevation of transaminase levels) or symptom (e.g., abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator. Laboratory reports will be initialed and dated on all pages by the Investigator.

Clinical Laboratory Tests Outside the Normal Range: Any value outside the normal range will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during Screening is indicated as clinically significant and is not covered by the inclusion or exclusion criteria in Section 8, the subject will **not** be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the EOS visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalised or stabilised.

All on-site ECG tracings and ECG over-read reports will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated on all pages by the Investigator.

12.3. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All pre-treatment events and AEs/all AEs must be recorded on the CRF.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- **Mild** - Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** - Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** - Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the study treatment:

- **Drug Interrupted** – Study drug stopped temporarily.
- **Drug Withdrawn** – Study drug stopped permanently.
- **Dose Not Changed**
- **Not Applicable.**
- **Unknown**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**

- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**
  - **Not related -** Improbable temporal relationship and is plausibly related to other drugs or underlying disease.
  - **Unlikely -** occurred within a reasonable time frame after administration/discontinuation of the study drug, but there is a likely association of an intercurrent/underlying medical condition or other drugs.
- **Related**
  - **Possible** - occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** - occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** - occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

12.4. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after first administration of study drug through 30 days following the last dose of the study medication, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form.

Following the end of subject participation in the study, the Investigator or an authorized delegate should report SAEs “spontaneously” to PPD-PVG if considered at least possibly related to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

In addition to the initial notification, an initial SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG within 1 business day of the Investigator or study center staff becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. PPD-PVG provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB) by the Principal Investigator or the appropriate person at the study center if required per IRB guidelines.

12.4.2. Pregnancy

Pregnancies that occur from the time of informed consent/assent through 30 days following the last dose of the study medication will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she/parent/legal guardian will be instructed to commence discontinuation of the study medication. Further, the subject/ parent/legal guardian (or female partner of male subject) will be instructed to return promptly/within 48 hours of the first notification of pregnancy to the study center and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the female pregnant subject will no longer receive any additional study medication. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD-PVG within 1 business day of the Investigator or study center staff becoming aware of the pregnancy. The Sponsor provides the Pregnancy Event Form.

If the subject received blinded study medication, unblinding of the study medication will be offered to the subject when knowledge of such treatment may have an impact on further treatment decisions. Otherwise, information regarding to what treatment the subject was assigned may be provided when the study has ended.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

12.5. Data and Safety Monitoring Board

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.

13. TERMINATION OF SUBJECT FROM STUDY/DISCONTINUATION OF STUDY DRUG

13.1. Criteria for Subject Termination

Subjects may terminate the study participation at any time for any reason.

The possible reasons for the termination of study participation are as follows:

- Adverse event.
- Lack of efficacy (specify).
- Lost to follow-up (specify).
- Pregnancy.
- Withdrawal by subject (specify).
- Non-compliance with study drug (specify).
- Protocol deviation (specify).
- Death.
- Other (specify).

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (e.g., experiences an AE, becomes pregnant), the subject must be discontinued from the study treatment.

The reason for discontinuation and information will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

Subjects who prematurely terminate the study participation may be replaced.

Subjects who discontinue study drug prior to completion will be asked to return to the clinic and complete the EOS visit 7 (± 2) days later (Section 11.5.3).

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center or at multiple centers for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, all documentation and study medications pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

In the event of study or site termination, subjects will be required to return to the clinic and complete the EOS visit 7 (± 2) days after their last dose of study drug and provided with access to standard care.

15. STATISTICS

An analysis of covariance (ANCOVA) will be applied to evaluate the treatment effect for the primary efficacy endpoint between the dasotraline 2 mg/day and placebo groups for the intent-to-treat (ITT) population. The model will include treatment, mean SKAMP-Combined score at baseline, and site as fixed effects. The primary efficacy analysis will be repeated for the per protocol (PP) population. To explore the robustness of the primary efficacy analysis of change from baseline at Day 15 in ADHD symptoms in mean SKAMP-Combined score, 2 sensitivity analyses will be performed, a placebo-based multiple imputation pattern-mixture model (PMM) and a tipping point analysis using the PMM.

A similar ANCOVA model, as described above, will be used for the secondary efficacy endpoints for the ITT population.

The Statistical Analysis Plan (SAP) will provide details on the statistical methods planned for this study and will be finalized before the study database lock (DBL).

15.1. Sample Size

A post-hoc ANCOVA-LOCF analysis of data from the SEP360-305 laboratory classroom study was conducted to examine the effect of dasotraline 4 mg/day versus placebo in a subset of pediatric patients with ADHD aged 6-9 years old. This analysis showed an effect size in this subgroup of 0.95 (LS mean difference at Week 2 was 7.2 with a standard error of 2.2). Assuming a smaller effect size for dasotraline 2 mg/day vs. placebo than that of dasotraline 4 mg/day vs. placebo, an effect size of 0.7 was utilized for the sample size calculation.

The .7 effect size also derives from a data analysis showing that in a weight-adjusted dose range of 0.065 mg/kg to 0.115 mg/kg , the SKAMP effect size was observed to be 0.70. The weight adjusted dosing in the proposed study (SEP360-311) will likely range from 0.057 mg/kg to 0.125 mg/kg given that six year old females are expected to be the lightest subjects (CDC estimates 16 kg = 3rd percentile). Thus, the estimated effect size of .7 is a reasonable assumption and will be employed in the power and sample size calculation.

Therefore, assuming an effect size of 0.7 for dasotraline 2 mg/day compared to placebo on the primary efficacy endpoint of mean SKAMP-Combined score obtained from the average of 7 assessments collected across the 12 hour classroom day, 88 subjects (44 per treatment group) will provide 90% power to detect a treatment effect between dasotraline and placebo at the two-sided alpha level of 0.05, based on the two-sample t-test with equal variance procedure.

The study will target approximately 100 subjects (50 per treatment group) randomized to either placebo or dasotraline 2 mg/day in an attempt to have 88 subjects complete the trial (assuming a 12% overall dropout rate).

15.2. Analysis Populations

The analysis populations are defined below. Subjects will be analyzed based on the treatment to which they are randomly assigned.

ITT (Intent-to-Treat) population: The ITT population is defined as all subjects who are randomized. The ITT population will be used for the efficacy analyses.

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.

Per Protocol (PP) population: The PP population will consist of all subjects from the ITT population without any important protocol deviation (see Section 15.3.3). This supplemental efficacy population will be used to assess robustness of the primary analysis results.

15.3. Data Analysis

15.3.1. Subject Disposition

Subject disposition will be summarized for all randomized subjects. Subjects who complete the study and discontinue from the study will be summarized. The reason for discontinuation from the study will also be presented.

15.3.2. Drug Exposure and Compliance

A descriptive summary will be performed for exposure to study medication. Treatment compliance will be determined and summarized descriptively using the safety population.

15.3.3. Important Protocol Deviations

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

A summary of protocol deviations will be provided as number (%) of subjects with at least 1 protocol deviation and number (%) of subjects in each category in all randomized subjects.

The definition of important protocol deviations will be detailed in the study SAP and the subjects with important protocol deviations will be pre-identified (prior to unblinding of the study).

15.3.4. Demographic and Baseline Characteristics

Demographics (sex, race, ethnicity, age [years], baseline weight [kg], height [cm], and BMI [kg/m^2]) will be summarized 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.

15.3.4.1. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The count and percentage of subjects under each history term, coded by system organ class (SOC) and preferred term (PT) will be summarized using the safety population.

15.3.4.2. Psychiatric History

Psychiatric history will be summarized by DSM-5. The count and percentage of subjects under each DSM-5 code will be summarized using the safety population.

15.3.4.3. Family Psychiatric History

Family psychiatric history, as reported by the parent/guardian, will be summarized by DSM-5. The count and percentage of subjects with any first degree relative (biological parent or sibling) considered to have a DSM-5 disorder will be summarized under the DSM-5 disorder deemed most appropriate by the rater, using the safety population.

15.3.5. Efficacy Analyses

15.3.5.1. Primary Efficacy Endpoint Analysis

The primary endpoint of change from baseline at Day 15 in ADHD symptoms as measured by mean SKAMP-Combined score obtained from an average of the 7 assessments collected across the 12-hour classroom day (12 to 24 hours postdose) will be evaluated.

An analysis of covariance (ANCOVA) model will be applied to evaluate the treatment effect for the primary efficacy endpoint between the dasotraline 2 mg/day and placebo groups for the ITT population. The model will include treatment, mean SKAMP-Combined score at baseline, and site as fixed effects.

In addition, the primary efficacy analysis will be repeated for the PP population.

15.3.5.2. Secondary Efficacy Endpoint Analysis

A similar ANCOVA model, as described above, will be used for the secondary efficacy endpoints for the ITT population.

- 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 postdose) 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 postdose)
- 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 postdose) 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 postdose)
- 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 postdose) during the classroom day

- Change from baseline at Day 15 in PERMP-Attempted and Correct Problems scores at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours postdose) during the classroom day
- Mean SKAMP-Combined score from the 7 assessments collected across the 12 hour classroom day (12 to 24 hours postdose) on Day 15
- SKAMP-Combined score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours postdose) during the classroom day on Day 15
- SKAMP-Attention subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours postdose) during the classroom day on Day 15
- SKAMP-Deportment subscale score at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours postdose) during the classroom day on Day 15
- PERMP-Attempted and Correct Problems scores at each of the assessment times (12-, 14-, 16-, 18-, 20-, 22-, and 24-hours postdose) during the classroom day on Day 15
- Change from baseline at Day 15 in mean PERMP-Attempted score obtained from an average of the 7 assessments collected across the 12-hour classroom day (12 to 24 hours postdose).
- Change from baseline at Day 15 in mean PERMP-Correct score obtained from an average of the 7 assessments collected across the 12-hour classroom day (12 to 24 hours postdose).
- Secondary weight based efficacy analyses will also be conducted on the SKAMP and PERMP.

15.3.5.3. Adjustment for Multiplicity

There will be no adjustment for multiplicity for the primary efficacy analysis, secondary efficacy analyses, or safety analyses.

15.3.5.4. Subgroup Analysis

The following safety analyses will be performed using the ITT population.

- Gender
- Race
- Age group (6 - 9 years and 10 - 12 years).

15.3.6. Safety Analyses

All safety analyses will be performed on the safety population. Unless specifically 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.

15.3.6.1. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher. AEs are untoward medical occurrences:

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

AEs will be summarized by treatment and by MedDRA system organ class (SOC) and Preferred Term (PT).

The following AEs will be summarized and presented by treatment group and by MedDRA SOC and PT for the Safety population:

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

The following conventions will be followed in summarizing AEs:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.
- If a subject reports more than one AE within a preferred term and/or a body system, the AE with the highest known severity within each body system and within each preferred term will be included in the summaries by severity.
- 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."

A listing of AEs, as well as a listing of deaths, SAEs, or AEs leading to discontinuation, will be presented.

A listing of AEs of special concern and AEs leading to discontinuation, stratified by weight, will be presented.

15.3.6.2. Clinical Laboratory Assessments

Summary statistics for protocol-specified laboratory parameters (hematology, serum chemistry, and urinalysis) will be provided. Laboratory data will also be summarized by presenting shift tables, by presenting summary statistics of raw data and change from baseline values (means, standard deviations, medians, ranges), and by the flagging of abnormal values in data listings.

15.3.6.3. ECGs

Electrocardiogram interval data (ventricular heart rate, RR, PR, QRS, QT, QTc, QTcB, and QTcF) will be summarized using descriptive statistics for baseline, each postdose evaluation, and change from baseline to each postdose evaluation.

15.3.6.4. Vital Signs

Vital signs (respiratory rate, body temperature, supine and standing blood pressure, supine and standing pulse rate, body weight) will be summarized at each visit for the absolute value and change from baseline using descriptive statistics.

15.3.6.5. Neurological Examination

Neurological examination assessments will be summarized using summary statistics for categorical variables (normal/abnormal) by visit. A shift table for baseline condition vs the worst result during the course of the study period (Abnormal > Normal) will be presented by treatment.

15.3.6.6. Concomitant Medications

All medications will be coded using World Health Organization drug dictionary (WHO-DD).

The prior medications will include medications reported by the subject that started within 30 days prior to screening. The concomitant medications will include medications started on or after the first dose date of study drug

Frequency counts and percentages of previous and concomitant medications will be presented by the WHO-DD Anatomic Therapeutic Chemical (ATC) classification and preferred term for each subject group.

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

The number of subjects having any suicidal behavior or suicidal ideation from the C-SSRS evaluation will be summarized.

15.3.6.8. Subgroup Analysis

No subgroup analysis will be conducted for safety endpoints.

15.3.7. Treatment of Missing Data

Missing data handling for efficacy endpoints will be detailed in the statistical analysis plan (SAP). No missing data handling will be applied for safety endpoints.

15.3.8. Sensitivity Analyses

To explore the robustness of the primary efficacy analysis of change from baseline at Day 15 in ADHD symptoms in mean SKAMP-Combined score, 2 sensitivity analyses will be performed, a placebo-based multiple imputation pattern-mixture model (PMM) and a tipping point analysis using the PMM. The detail of the sensitivity analyses will be documented in the final SAP.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL /DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results) will be recorded in the subject's electronic CRF. K-SADS-PL, C-SSRS, ADHD-RS-IV HV, SKAMP, and PERMP will be completed on paper and then entered into the electronic data capture (EDC) system. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11, Medidata Rave®. Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

16.2. Computerized Systems Used for Source Data

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are presented below, pursuant to the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

Table 7: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Obtain informed consent	A
Obtain informed assent	A
Inclusion/Exclusion criteria	A
Randomization	A,D
Dispense study drug	A,D
Study drug accountability	A
Medical History	A
Psychiatric History	A
Prior/concomitant medication review	A
K-SADS-PL	A
Physical examination	A
Neurological examination	A
Height	A
Weight (including body mass index)	A
Vital signs	A

Table 7: Computerized Systems Used for Source Data (Continued)

Protocol Step	Computerized System Type or Description
Electrocardiogram (ECG)	C
Adverse event monitoring	A
Columbia Suicide Severity Rating Scale (C-SSRS)	A
ADHD-RS-IV HV	A
Classroom Practice Session	A
SKAMP	A
Math pretest for determination of math level	A
PERMP	A
Dosing diary distribution/review	A
Hematology/Chemistry	B
TSH	B
Serum β-hCG (in females ≥ 8 years of age)	B
Urinalysis	B
Urine drug screen	A
Urine β-hCG (in females ≥ 8 years of age)	A
Statistical analysis	SAS®, version 9 or higher

A = EDC (Medidata Rave®); B = LIMS; C = Core Lab Over-read; D = IXRS.
Abbreviations: ADHD-RS-IV HV = ADHD Rating Scale Version IV Home Version (modified for investigator administration), β-hCG = beta-human chorionic gonadotropin, EDC = electronic data capture; IXRS = interactive recognition system; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime version, LIMS = laboratory information management system, PERMP = Permanent Product Measure of Performance, SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale, TSH = thyroid stimulating hormone.

16.3. Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with International Conference on Harmonization (ICH) Good Clinical Practice (GCP). On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.4. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent/assent by signing the informed consent form (ICF)/ informed assent form (IAF). By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study

documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

16.5. Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.6. Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis for most of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification, lab director’s curricula vitae and a current, dated copy of normal range values.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the “Investigator Approval" page.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license, current Drug Enforcement Agency (DEA) license, where applicable), and financial disclosure information. In countries where medical licensure is not issued, the following documentation is acceptable, as applicable:

- Registration number/stamp with a registration number stated on curriculum vitae.
- Appropriate diploma number stated on curriculum vitae.
- Copy of the diploma.

The Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to Sponsor/CRO.

17.2. Institutional Review Board

Documented approval for conducting the study from appropriate Institutional Review Board (IRB) will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB approval must be obtained and also forwarded to the Sponsor. The IRB must supply the Sponsor a list of the IRB membership, and a statement to confirm that the IRB is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB chairman or designee identify the IRB name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB complies with the requirements in 21 CFR Part 56 for a study conducted under a US Investigational New Drug (IND) or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally specified by the

IRB. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3. Informed Consent

The informed consent form and informed assent form will be approved by the Sponsor/CRO prior to submission to the IRB. The Sponsor/CRO may provide a template informed consent/ informed assent form to be qualified by each research facility to conform to local requirements. All informed consent/assent forms must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB approval. The Sponsor/CRO may submit informed consent forms to a central IRB for review and approval or favorable opinion contingent upon prior Investigator permission and review.

Before recruitment and enrollment, each prospective subject/parent/legal guardian will be given a full explanation of the study, allowed to read the approved informed consent form and assent form(s), as appropriate, and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject/parent/legal guardian understands the implications of participating in the study, the prospective subject and at least one parent/legal guardian will be asked to give consent to participate in the study by signing the informed consent and assent form(s), as appropriate. As part of the consent process, each prospective subject and at least one parent/legal guardian must consent to direct access to the subject's medical records for study-related monitoring, auditing, IRB review, and regulatory inspection. It should be clearly explained to each prospective subject/parent/legal guardian that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study medication, but that does not necessarily negate the expectation that the subject/parent/legal guardian will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form and assent forms to each subject/parent/legal guardian, and will record the date of the informed consent and assent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's parent's/legal guardian's consent/assent, the informed consent/assent form(s) must be revised, submitted to the IRB for review and approval or favorable opinion. The revised informed consent/assent form(s) must be used to obtain consent/assent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent/assent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Subject Privacy

The Sponsor (or Sponsor representative) or any designees affirm uphold the subjects confidentiality. The subject will be identified by unique code only; full names will be masked

prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

17.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB immediately/within 5 business days of the occurrence, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 15 years from time of participation in the study or longer in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor and its representative and, the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

17.9. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the

Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

18. REFERENCES

Amor LB, Grizenko N, Schwartz G, Lageix P, Baron C, et al. Perinatal complications in children with attention-deficit hyperactivity disorder and their unaffected siblings. Rev Psychiatr Neurosci 2005;30(2):120-6.

Arnsten AF, Pliszka SR. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol Biochem Behav 2011;99:211-6.

Aron AR, Poldrack RA. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;7:1285-92.

Boonstra AM, Oosterlaan J, Sergeant JA, Buitelaar JK. Executive functioning in adult ADHD: a meta-analytic review. Psychol MEd 2005;35:1097-1108.

Botting N, Powls A, Cooke RWI. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. J Child Psychol Psychiat 1997;38(8):931-41.

Childress AC, Brams M, Kollins SH, Northcutt J, Padilla A, Turnbow JM. The efficacy and safety of Evekeo, racemic amphetamine sulfate, for treatment of attention-deficit/hyperactivity disorder Symptoms: A multicenter, dose-optimized, double-blind, randomized, placebo-controlled crossover laboratory classroom study. Journal of Child and Adolescent Psychopharmacology. 2015;25(5):402-14.

Ferri FF. Attention deficit hyperactivity disorder. Ferri's Clinical Advisor 2015. St. Louis, MO: Mosby, an imprint of Elsevier; 2014:160-1.

Gamo NJ, Arnsten AF. Molecular modulation of prefrontal cortex: rational development of treatments for psychiatric disorders. Behav Neurosci 2011;125:282-96.

Goto Y, Hatakeyama K, Kitama T, Sato Y, Kanemura H, et al. Saccade eye movements as a quantitative measure of frontostriatal network in children with ADHD. Brain Dev 2010;32:347-55.

Hannestad J, Gallezot JD, Planeta-Wilson B, Lin SF, Williams WA, van Dyck CH, et al. Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. Biol Psychiatry 2010;68:854-60.

Hervey AS, Epstein JN, Curry JF. Neuropsychology of Adults with Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Neuropsychology 2004; 18;485-503.

Koblan KS, Hopkins SC, Sarma K, Gallina N, Jin F, et al. Assessment of human abuse potential of dasotraline compared to methylphenidate and placebo in recreational stimulant users. Drug and Alcohol Dependence 2016;159:26–34.

Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA. Maturation of cognitive processes from late childhood to adulthood. Child Dev 2004;75:1357-72.

Passarotti AM, Pavuluri MN. Brain functional domains inform therapeutic interventions in attention deficit/hyperactivity disorder and pediatric bipolar disorder. Expert Rev Neurother 2011;11:897-14.

Perricone G, Morales MR, Anzalone G. Neurodevelopmental outcomes of moderately preterm birth: precursors of attention deficit hyperactivity disorder at preschool age. SpringerPlus 2013;22:221.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007;164(7):1035-43.

Rader R, McCauley L, Callen EC. Current strategies in the diagnosis and treatment of childhood attention-deficit/hyperactivity disorder. Am Fam Physician 2009;79(8):657-65.

Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 1998;155:1325-31.

Wigal S, Greenhill L, Nordbrock E, Connor D, Kollins SH, Adjei A, Childress A, Stehli A, Kupper R. A randomized placebo-controlled double-blind study evaluating the time course of response to methylphenidate hydrochloride extended-release capsules in children with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology 2014;24(10):562-9.

Wigal SB and Wigal TL. The Laboratory School Protocol: Its Origin, Use, and New Applications. J Atten Disord 2006;10; 92-111.

Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. Biol Psychiatry 2005:57;1336-46.

19. INVESTIGATOR APPROVAL

I have read the protocol, SEP360-311, Version 3.00, "Dasotraline (2mg) in Children Aged 6 to 12 Years with Attention-Deficit Hyperactivity Disorder (ADHD): A Randomized, Multicenter, Double-blind, Placebo-controlled, Parallel-group Study of Efficacy and Safety in a Laboratory Classroom Setting", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

ECG equipment and supplies will be provided by ECG Vendor and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The study center personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol that is provided by the cardiac safety vendor.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested 5 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study.
- ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the study center for review and signature.
- The ECG tracing will be kept with subject's source documentation and / or CRF unless it is specified otherwise. The original ECG and the cardiologist's over-read will be retained at the study center.

4. Data Standardization

ECG data will be transmitted to a centralized cardiac safety vendor and centrally over-read and interpreted using standardized procedures.

21. APPENDIX II. BODY MASS INDEX DETERMINATION

Body mass index (BMI) will be calculated by measuring the subject's height and weight (both determined without subject wearing shoes) and using these measurements (in centimeters and kilograms) in the following formula.

Formula:

BMI = weight (kg) ÷ [height (m) x height (m)]

BMI will be automatically calculated at screening by EDC, and not by the site staff.

22. APPENDIX III. CLINICAL LABORATORY TESTS

The following clinical laboratory tests are to be performed.

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)
Hemoglobin, Hematocrit, Platelet Count, RBC Count, WBC - Total Count, WBC Differential, (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: Thyroid stimulating hormone (TSH)

URINE DRUG SCREENING: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Cotinine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

OTHER TESTS: Serum Pregnancy (β-HcG) (in female subjects only ≥ 8 years of age), Urine Pregnancy Test (in female subjects only ≥ 8 years of age)

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

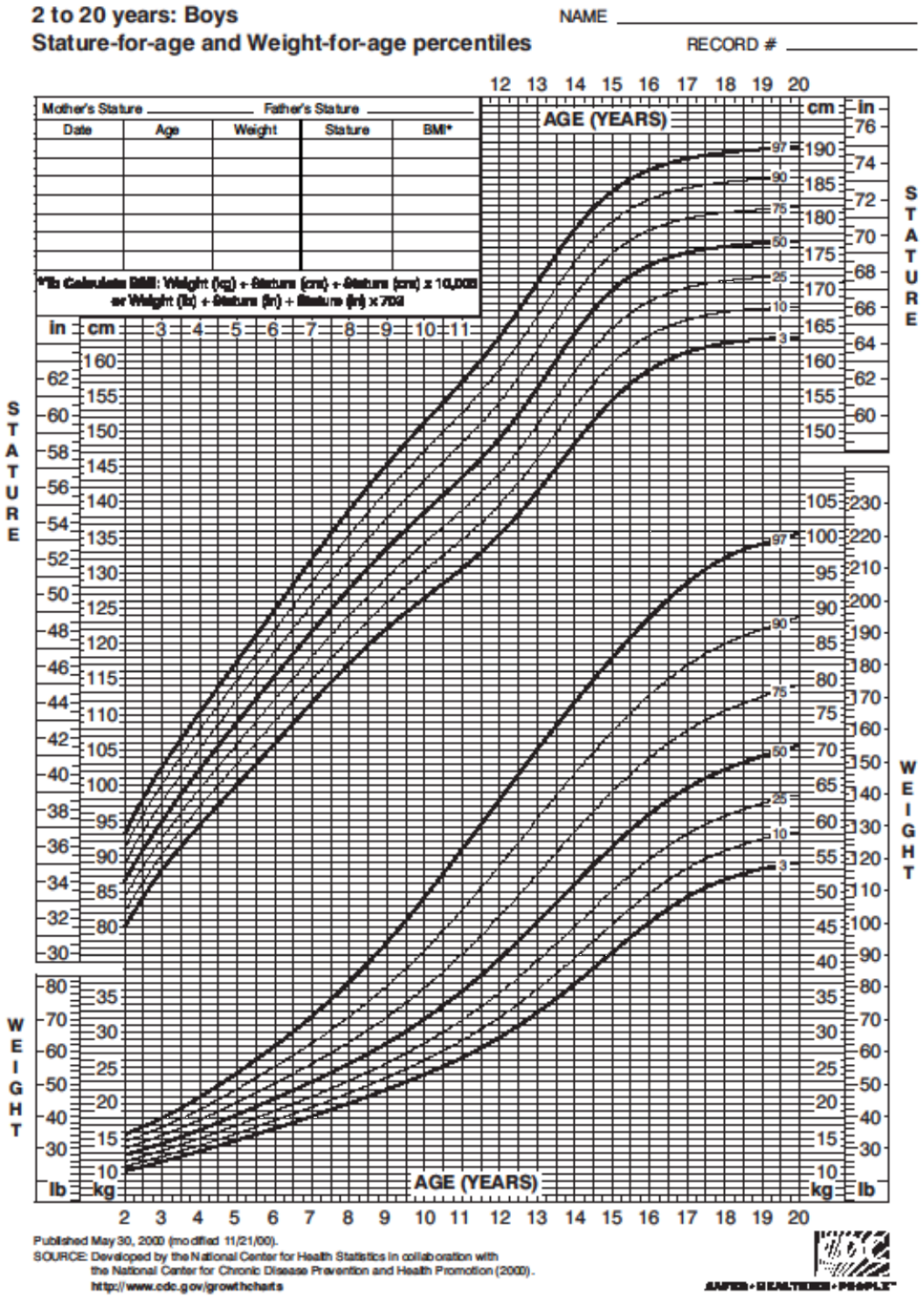
23. APPENDIX IV. CLINICALLY RELEVANT CYP2B6 SUBSTRATES OR INDUCERS OR INHIBITORS (GENERIC NAMES)

The following drugs are prohibited during this study.

Substrate	Inhibitor	Inducer
artemisinin	clopidogrel	artemisinin
bupropion	thiotepa	carbamazepine
cyclophosphamide	ticlopidine	efavirenz
efavirenz	voriconazole	nevirapine
ifosphamide		phenobarbital
Ketamine		phenytoin
meperidine		rifampin
methadone		
nevirapine		
Propafol		
Selegiline		
sorafenib		

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Accessed 4 March 2016.

24. APPENDIX V. GROWTH CHART (MALE).



25. APPENDIX VI. GROWTH CHART (FEMALE).