Dasotraline

Protocol SEP360-310

An Open-label, Flexibly-dosed, 26-Week Extension Safety Study of Dasotraline in Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD)

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician		Telephone: Fax: Email:
Medical Monitor		Office Telephone: Mobile Telephone: Fax: Email:
SAE/Pregnancy Reporting		Fax: Email:

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: Dasotraline (SEP-225289)

Title of Study: An Open-label, Flexibly-dosed, 26-Week Extension Safety Study of Dasotraline in Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD)

Proposed Indication: Attention Deficit Hyperactivity Disorder (ADHD)

Study Centers: Approximately 40 centers in the United States

Phase of Development: 3

Study Objectives:

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

Secondary:

- To evaluate the long-term safety and tolerability of flexibly-dosed dasotraline in children and adolescents with ADHD by assessing clinical laboratory evaluations, vital signs, physical examinations, body height and weight, 12-lead electrocardiograms (ECG), Tanner Staging, Children's Sleep Habits Questionnaire (CSHQ), and the frequency and severity of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS) Children's Assessment.
- To assess the long-term effectiveness of dasotraline in children and adolescents with ADHD using the following assessments:
    - ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV)
    - Clinical Global Impression – Severity (CGI-S)
    - Conners 3rd Edition Parent (Conners 3-P)
- To evaluate health-related quality of life and functional impairment in children and adolescents with ADHD using the Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P).
- To assess potential withdrawal symptoms following discontinuation of dasotraline treatment using the following assessments (administered during the withdrawal period):
    - Discontinuation-Emergent Signs and Symptoms (DESS) Scale
    - Physician Withdrawal Checklist (PWC)

Study Design:

This is an open-label, flexibly-dosed, 26-week extension study in children and adolescents with ADHD who have completed 6 weeks of double-blind treatment in the core study (SEP360-202). This study will evaluate the long-term safety and tolerability of dasotraline in this population. In addition, several measures of effectiveness will be included. Subjects who have completed the core study (ie, completed 6-week visit) will be eligible to enroll in this extension study; subjects who discontinue from the core study will not be eligible to enroll in this study. Subjects will be evaluated for eligibility in this

extension study during the Week 6 visit of the core study. Informed assent by the subject and informed consent from at least one of the subject's parents or legal guardians will be obtained before any study procedures are performed for this study.

Subjects who meet all eligibility criteria will transition directly from the core study and will not need to complete the End of Study (EOS) visit in the core study. Subjects will take the first dose of open-label study drug in this extension study on Day 1, the morning following the open-label (OL) Baseline visit. Subjects will continue to take study drug for 26 weeks, at approximately the same time each morning including on the days when clinic visits occur. Dasotraline will be dosed at 2 mg/day for the first week of the study (Days 1 – 7). Subjects will then be flexibly dosed (2, 4, or 6 mg/day) thereafter beginning on Day 8 based on the investigator's assessment of effectiveness and tolerability. All changes in study drug dose will begin the morning after the visit at which the dose change decision is made using the new package of study drug. Additional dose adjustment is allowed during the study at the discretion of the investigator; the dose may be increased or decreased by 2 mg/day, as necessary for effectiveness or tolerability reasons. Total daily dose will not exceed 6 mg/day. There is no limit on the number of dose increments or reductions during the study. A minimum of 7 days is required between dose increases. Dose decreases may be made at less than 7 day intervals for safety/tolerability reasons, at the investigator's discretion. Subjects wishing to take study drug at an alternate time of day require investigator and medical monitor approval.

After the OL Baseline visit, subjects will return to the clinic weekly for the first 2 weeks, once every 2 weeks for the next 4-weeks, then once every 4 weeks for the remainder of the treatment period for clinical evaluation, and once at the end of the withdrawal period (Visit 13E). At the approximate midpoint between the scheduled monthly visits (ie, 14 ± 2 days after a visit) during the treatment period, the site staff will contact the subject's parent/legal guardian via telephone, text, or email in order to evaluate the safety of the subjects as well as to remind subject/parent/legal guardian about adherence to study drug administration and upcoming visits, following which, if necessary, an unscheduled visit can be arranged.

Safety and tolerability will be monitored throughout the study by collection of AEs, clinical laboratory evaluations, vital signs, physical examinations, body height and weight, 12-lead ECG, Tanner Staging, CSHQ, and the frequency and severity of suicidal ideation and suicidal behavior using C-SSRS. The measures of effectiveness, ADHD-RS-IV HV, CGI-S, and Conners 3-P, and assessment of health-related quality of life and functional impairment, WFIRS-P, will be completed as scheduled (Table 2).

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

Assessment of potential withdrawal effects will be conducted via administration of the DESS and PWC at the end of study drug treatment (Visit 10E) and upon the completion of the withdrawal period (Visit 13E). In addition, the subject/parent/legal guardian will be called by the clinical site staff once a week (Day 189 ± 3 and Day 196 ± 3) during the withdrawal period to complete the DESS. Phone contacts may be made up to 3 times per day if the clinical site staff is unable to contact the subject/parent/legal guardian on the first 2 attempts. If the subject/parent/legal guardian cannot be contacted on a given day, during the next contact the study site staff will retrospectively collect the missed DESS, in addition to the current day's DESS, as necessary. Clinical site staff will record the responses in the subject's source information and in the CRF with the contact date and time. As noted above, all subjects will return to the clinic 3 weeks (± 7 days) after the final dose of study drug for withdrawal (DESS and the PWC) and EOS safety assessments (Visit 13E).

Subjects who discontinue from the study prior to completion will be asked to return to the clinical site and complete the Early Termination assessments within 3 days of discontinuation and complete all withdrawal period assessments (calls) and EOS visit.

After the EOS visit or upon discontinuation of study drug, all subjects will be referred for continuation of their care as determined by the investigator.

Number of Subjects (planned): This study is projected to enroll up to 330 subjects based on the number of subjects who complete the core study.

Diagnosis and Main Criteria for Subject Inclusion:

Eligibility criteria will be assessed at the OL Baseline visit (Week 6 in the core study). Assessments performed as part of the Week 6 visit in the core study do not need to be repeated.

Inclusion Criteria:

1. 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 complete an informed assent prior to study participation.
2. Subject and subject's parent/legal guardian are judged by the investigator to be willing and able to comply with the study procedures and visit schedules.
3. Subject has completed all required assessments for Week 6 of the core study.
4. Subject has not taken any medication other than the study drug for the purpose of controlling ADHD symptoms during the core study.
5. Subject, if female, must not be pregnant or breastfeeding.
6. Female subject:
   - must be unable to become pregnant (eg, premenarchal, surgically sterile, etc);

   -OR-

   - practice true abstinence (consistent with lifestyle) and must agree to remain abstinent from signing informed consent/assent to at least 14 days after the last dose of study drug has been taken;

   -OR-

   - is sexually active and willing to use a medically effective method of birth control (see Appendix IV, Section 23) from signing informed consent/assent to at least 14 days after the last dose of study drug has been taken.
7. Male subject must be willing to remain sexually abstinent (consistent with lifestyle) or use an effective method of birth control (see Appendix IV, Section 23) from signing informed consent/assent to at least 14 days after the last dose of study drug has been taken.
8. Any subject whose weight is < 21 kg at the OL Baseline visit should be discussed with the medical monitor prior to enrollment.
9. Subject and subject's parent/legal guardian must be able to fully comprehend the informed consent/assent form (as applicable), understand all study procedures, and be able to communicate satisfactorily with the Investigator and study coordinator.

Exclusion Criteria:

1. Subject is considered by the investigator to be at imminent risk of suicide, injury to self or to others, or damage to property.
2. 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 "Since Last Visit" assessment at OL

Baseline.

3. Subject has a clinically significant abnormality including physical examination, vital signs, ECG, or laboratory tests that the investigator in consultation with the medical monitor considers to be inappropriate to allow participation in the study.
4. Subject has a positive urine drug screen (UDS) or breath alcohol test at OL Baseline.
5. Subject or parents/legal guardian has commitments during the study that would interfere with attending study visits.
6. Subject is at high risk of non-compliance in the investigator's opinion.

Investigational Product, Dosage and Mode of Administration: Dasotraline 2, 4, and 6 mg capsules for oral administration will be supplied. One capsule of study drug will be taken once daily for 26 weeks (Day 1 through Day 182), at approximately the same time each morning without regard for food including on the days when clinic visits occur. If morning dosing is not tolerated then dosing may be at another time of day with prior medical monitor approval; however, if there is a time of day dosing change, subjects should administer study drug at the same time of day for the remainder of the study.

Dose schedule and adjustment are described under Study Design.

Duration of Treatment: 26 weeks

Reference Therapy, Dosage and Mode of Administration: Not applicable

Concomitant Medications:

Disallowed Medications During Study

Use of any of the following medications is not permitted during the study through EOS: lithium (any lithium preparation or formulation); alpha-2 adrenergic receptor agonists (including clonidine and guanfacine), modafinil, armodafinil, atomoxetine, or any stimulant class (methylphenidate- or amphetamine-based) agent; antidepressant medications and St. John's Wort; anticonvulsant medications and antipsychotic medications; pseudoephedrine-containing medications for treatment of allergies or flu-like symptoms; 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 ≤ 5 mg/day); any medications for the treatment of ADHD; and 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.

Other Treatment Restrictions:

Subjects undergoing cognitive behavioral therapy (CBT) are excluded from entering the study. In addition, a new course of CBT specifically for ADHD is not allowed during the study. 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.

Study Endpoints:

Primary Endpoint: The incidence of overall AEs (or serious AEs), and AEs (or serious AEs) leading to discontinuation.

Secondary Endpoints:

- Clinical laboratory evaluations (serum chemistry, hematology, lipid panel, thyroid function panel, urinalysis, sex hormones).
- Clinical evaluations (vital signs, physical examination, body height and weight, Tanner

Staging, and 12-lead ECG).

- Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS.
- Change in CGI-S score.
- Change in ADHD-RS-IV HV total score.
- Change in the inattentiveness and hyperactivity subscales of the ADHD-RS-IV HV.
- Change in Conners 3-P total score and subscale scores (Oppositional, Cognitive problems, Hyperactivity, and ADHD Index).
- Change in CSHQ total score and 8 subscale scores (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness).
- Change in WFIRS-P total score and 6 domain scores (family, school learning behavior, life skills, child's self-concept, social activities, and risky activities).
- Symptoms of withdrawal using:
    - PWC score
    - DESS score

Statistical Methods:

No statistical inference will be performed for treatment comparisons as this is a single arm, open-label, extension study. Continuous variables will be summarized using descriptive statistics of number of subjects, mean, standard deviation, median, minimum and maximum values. Categorical variables will be reported as frequencies and percentages. All statistical summaries will be presented by treatment group in the double-blind study as well as all subjects in the extension study. Changes from baseline in safety and effectiveness endpoints will be calculated from both the double-blind (DB) baseline in the core study and the OL baseline in the extension study, which is Week 6 endpoint in the core study.

The summary of AEs and serious AEs will be limited to treatment emergent AEs (TEAE). The TEAEs will be summarized by system organ class (SOC) and preferred term (PT) by presenting the number and percentage of subjects with any TEAE. Descriptive statistics also will be provided by visit based on observed values and changes from baselines for the following safety variables: laboratory tests (hematology, chemistry, urinalysis, lipid panel, thyroid function panel, and sex hormones), vital signs, ECG parameters, Tanner staging, and CSHQ. Shift tables comparing OL baseline to end of study will be presented, as appropriate. In addition, the markedly abnormal post-baseline results will be summarized for certain safety parameters, as appropriate. The frequency and percentage by visit will be summarized for all C-SSRS responses.

The long-term effectiveness data will be summarized descriptively for the changes from baseline in ADHD-RS-IV HV total score and subscale scores, CGI-S score, and Conners 3-P total score and subscale scores.

The change from baseline in the WFIRS-P total score and its domain scores will be summarized.

The PWC and DESS will be summarized using descriptive statistics by visit for the total score.

Sample Size:

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

Table 2: Schedule of Assessments

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

Table 2: Schedule of Assessments (Continued)

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

Table 2: Schedule of Assessments (Continued)

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

Abbreviations: β-hCG = beta-human chorionic gonadotropin, EOS = end of study, ET = early termination, OL = open label

[a] Week 6 in core study. Baseline assessments indicated as "carried over" are performed as part of Week 6 visit in the core study (with the exception of medical and psychiatric history from screening in the core study) and do not need to be repeated; the data will be duplicated from Week 6 visit in the core study.

[b] Subjects who discontinue from the study prior to completion will be asked to return to the site and complete the ET assessments within 3 days of discontinuation and complete all withdrawal period assessments (calls) and EOS visit.

Footnotes are continued on the next page.

[c] Subjects will take the first dose of study drug in this study on Day 1, the morning following the baseline visit; there will be no break in study drug treatment between the core study and this extension study. All study drug will be administered by the subject in the morning. Subjects wishing to take study drug at an alternate time of day require investigator and medical monitor approval.

[d] At the approximate midpoint between the scheduled monthly visits during the treatment period, the site staff will contact the subject's parent/legal guardian via telephone, text, or email in order to evaluate the safety of the subject, as well as to remind subject/parent/legal guardian about adherence to study drug administration and upcoming visits, following which an unscheduled visit may be scheduled, if necessary. The date and time of these contacts will be documented in the case report form (CRF).

[e] 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.

[f] Thyroid-stimulating hormone (TSH), free T4, and free T3 will be evaluated.

[g] Subjects should be fasted (no food or drink except water at least 8 hours prior to blood draws for the lipid panel). Blood samples should be drawn in the morning followed by a snack or meal.

[h] For females: estradiol, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). For males: testosterone.

[i] Females ≥ 8 years of age. Any positive urine β-hCG test should be confirmed by serum β-hCG.

[j] Clinical site staff will call the subject/parent/legal guardian each week (Day 189 ± 3 and Day 196 ± 3) during the study medication withdrawal period in order to complete the Discontinuation-Emergent Signs and Symptoms (DESS). Clinical site staff may call up to 3 times per day if the clinical site staff are unable to contact the subject/parent/legal guardian on the first 2 attempts. If the subject/parent/legal guardian cannot be contacted on a given day, during the next contact the study site staff will retrospectively collect the DESS from the missed day and the current day, as necessary.

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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 3 and Table 4.

Table 3: List of Abbreviations

Abbreviation	Full Form
ADHD	Attention deficit hyperactivity disorder
ADHD-RS-IV HV	ADHD Rating Scale Version IV - Home Version (modified for investigator administration)
AE	Adverse event
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CBT	Cognitive behavioral therapy
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression–Severity of Illness
CIMS	Clinical Inventory Management System
Conners 3-P	Conners 3rd Edition Parent
CRF	Case report form
CRO	Contract research organization
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia Suicide Severity Rating Scale
CTM	Clinical trial material
DAT	Dopamine transporter
DBL	Database lock
DESS	Discontinuation-Emergent Signs and Symptoms
DHPG	3, 4-dihydroxyphenylglycol
DNRI	Dopamine and norepinephrine, reuptake inhibitor
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	US Food and Drug Administration

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
GCP	Good Clinical Practice
HR	Heart rate
IAF	Informed assent form
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ITT	Intention-to-Treat
IXRS	Interactive response system
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version
MAO	Monoamine oxidase
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
NET	Norepinephrine transporter
ODD	Oppositional defiant disorder
OL	Open-label
PK	Pharmacokinetic(s)
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
PWC	Physician Withdrawal Checklist
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
RR	RR interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
SOC	System organ class
TEAE	Treatment-emergent adverse event
UDS	Urine drug screen
WFIRS-P	Weiss Functional Impairment Rating Scale – Parent Report
WHODRUG	World Health Organization drug dictionary

Table 4: 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.
Study Drug (or Study medication)	Term to cover investigational drug.
Treatment Period	The period of the study in which the study drug is administered.
Completed Subject	Any subject who participated throughout the duration of the study, up to and including the last on-treatment visit (Week 26).
Early Termination Subject	Any subject who was successfully screened and enrolled into the treatment period of the study, but did not complete the study.
End of Treatment	The day that the subject receives 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, though 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, and perhaps to a lesser degree serotonin, are expected to have a critical role in the development of ADHD and thus receptors associated with these are key drug targets (Rader-2009). Changes in serotonergic, cholinergic, and mostly dopaminergic functioning have been documented in children with ADHD (Dopheide-2011).

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 dopamine transporter (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, unique among

ADHD treatments, allows plasma concentrations to remain in a therapeutic range over the 24 hour dosing interval at steady state.

The evaluation of the pharmacokinetics and safety of dasotraline in pediatric and adolescent subjects is currently ongoing (Study SEP360-105). Study SEP360-105 will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of dasotraline in subjects 6 – 17 years old with ADHD. It is a multicenter, open-label study in which subjects are assigned to study drug in a dose-escalating manner. The doses planned to be evaluated range from 1 - 32 mg. Additionally, the safety and efficacy of dasotraline in 6 – 12 year old subjects with ADHD is ongoing in a randomized, double-blind, multicenter, placebo-controlled, parallel-group, outpatient study (SEP360-202).

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

As there is a considerable unmet medical need for ADHD medications in children and adolescents that may warrant long-term treatment, 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

ADHD is prevalent in approximately 8% to 10% of school-aged children (Ferri-2014) and causes substantial impairments in everyday functioning that may warrant long-term treatment. A medication such as dasotraline that may provide therapeutic coverage across a 24-hour dosing interval may prove beneficial for the treatment of ADHD.

This is an open-label extension study to evaluate the safety and effectiveness of flexibly-dosed dasotraline over 26 weeks of treatment in children and adolescents with ADHD who completed 6 weeks of double-blind treatment in Study SEP360-202 (ie, the core study).

4.3. Risk-Benefit Assessment

Two studies were recently completed to support dasotraline as a safe and efficacious treatment for adults with ADHD 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. 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 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 change from baseline in 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. Treatment-emergent AEs (TEAEs) were consistent with dasotraline pharmacology, ie, insomnia, decreased appetite, dry mouth, and headache. Worsening of insomnia associated with

dasotraline was characterized by TEAEs, and shifts in Insomnia Severity Index (ISI) total score, particularly with dasotraline 8 mg/day. TEAEs, 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.

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, SEP360-101, evaluated dasotraline's abuse liability and was conducted in recreational stimulant users; results indicated that dasotraline has low abuse liability. 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 1 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) 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.

5. STUDY OBJECTIVES

5.1. Primary Objectives

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

5.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the long-term safety and tolerability of flexibly-dosed dasotraline in children and adolescents with ADHD by assessing clinical laboratory evaluations, vital signs, physical examinations, body height and weight, 12-lead electrocardiograms (ECG), Tanner Staging, Children's Sleep Habits Questionnaire (CSHQ), and the frequency and severity of suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS) Children's Assessment.
- To assess the long-term effectiveness of dasotraline in children and adolescents with ADHD using the following assessments:
  - the ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV)
  - the Clinical Global Impression – Severity (CGI-S)
  - the Conners 3rd Edition Parent (Conners 3-P)
- To evaluate health-related quality of life and functional impairment in children and adolescents with ADHD using the Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P).
- To assess potential withdrawal symptoms following discontinuation of dasotraline treatment using the following assessments (administered during the withdrawal period):
  - Discontinuation-Emergent Signs and Symptoms (DESS) Scale
  - Physician Withdrawal Checklist (PWC)

6. STUDY ENDPOINTS

6.1. Primary Endpoint

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

6.2. Secondary Endpoints

The secondary endpoints are:

- Clinical laboratory evaluations (serum chemistry, hematology, lipid panel, thyroid function panel, urinalysis, sex hormones).
- Clinical evaluations (vital signs, physical examination, body height and weight, Tanner Staging, and 12-lead ECG).
- Frequency and severity of suicidal ideation and suicidal behavior using the C-SSRS.
- Change in CGI-S score.
- Change in ADHD-RS-IV HV total score.
- Change in the inattentiveness and hyperactivity subscales of the ADHD-RS-IV HV.
- Change in Conners 3-P total score and subscale scores (Oppositional, Cognitive problems, Hyperactivity, and ADHD Index).
- Change in CSHQ total score and 8 subscale scores (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness).
- Change in WFIRS-P total score and 6 domain scores (family, school learning behavior, life skills, child's self-concept, social activities, and risky activities).
- Symptoms of withdrawal using:
  - PWC score
  - DESS score

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, flexibly-dosed, 26-week extension study in children and adolescents with ADHD who have completed 6 weeks of double-blind treatment in the core study. This study will evaluate the long-term safety and tolerability of dasotraline in this population. In addition, several measures of effectiveness will be included. Subjects who have completed the core study (ie, completed Week 6 visit) will be eligible to enroll in this extension study; subjects who discontinue from the core study will not be eligible to enroll in this study. Subjects will be evaluated for eligibility in this extension study during the Week 6 visit of the core study. Informed assent by the subject and informed consent from at least one of the subject's parents or legal guardians will be obtained before any study procedures are performed for this study.

Subjects who meet all eligibility criteria will transition directly from the core study and will not need to complete the End of Study (EOS) visit in the core study. Subjects will take the first dose of open-label study drug in this extension study on Day 1, the morning following the open-label (OL) Baseline visit. Subjects will continue to take study drug for 26 weeks, at approximately the same time each morning including on the days when clinic visits occur. Dasotraline will be dosed at 2 mg/day for the first week of the study (Days 1 - 7). Subjects will then be flexibly dosed (2, 4, or 6 mg/day) thereafter beginning on Day 8 based on the investigator's assessment of effectiveness and tolerability. All changes in study drug dose will begin the morning after the visit at which the dose change decision is made using the new package of study drug. Additional dose adjustment is allowed during the study at the discretion of the investigator; the dose may be increased or decreased by 2 mg/day, as necessary for effectiveness or tolerability reasons. Total daily dose will not exceed 6 mg/day. There is no limit on the number of dose increments or reductions during the study. A minimum of 7 days is required between dose increases. Dose decreases may be made at less than 7 day intervals for safety/tolerability reasons, at the investigator's discretion. Subjects wishing to take study drug at an alternate time of day require investigator and medical monitor approval.

After the OL Baseline visit, subjects will return to the clinic weekly for the first 2 weeks, once every 2 weeks for the next 4 weeks, then once every 4 weeks for the remainder of the treatment period for clinical evaluation, and once at the end of the withdrawal period (Visit 13E). At the approximate midpoint between the scheduled monthly visits (ie, 14 ± 2 days after a visit) during the treatment period, the site staff will contact the subject's parent/legal guardian via telephone, text, or email in order to evaluate the safety of the subjects as well as to remind subject/parent/legal guardian about adherence to study drug administration and upcoming visits, following which, if necessary, an unscheduled visit can be arranged.

Safety and tolerability will be monitored throughout the study by collection of AEs, clinical laboratory evaluations, vital signs, physical examinations, body height and weight, 12 lead ECG, Tanner Staging, CSHQ, and the frequency and severity of suicidal ideation and suicidal behavior using C-SSRS. The measures of effectiveness, ADHD-RS-IV HV, CGI-S, and Conners 3-P, and assessment of health-related quality of life and functional impairment, WFIRS-P, will be completed as scheduled (Table 2).

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

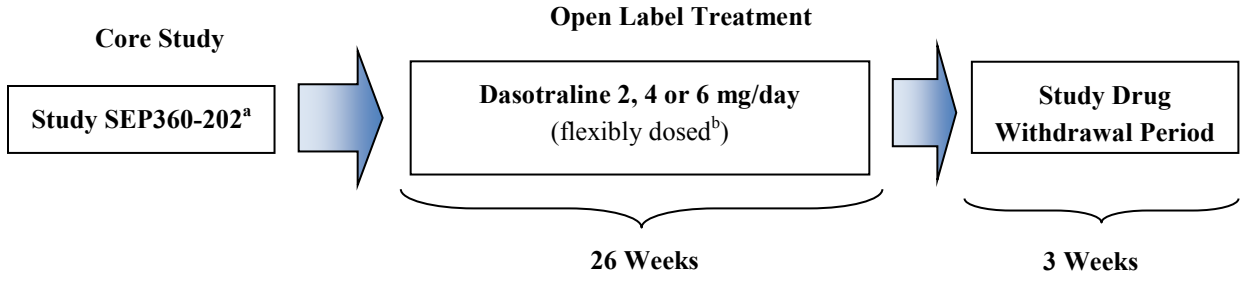
Assessment of potential withdrawal effects will be conducted via administration of the DESS and PWC at the end of study drug treatment (Visit 10E) and upon the completion of the withdrawal period (Visit 13E). In addition, the subject/parent/legal guardian will be called by the clinical site staff once a week (Day 189 ± 3 and Day 196 ± 3) during the withdrawal period to complete the DESS. Phone contacts may be made up to 3 times per day if the clinical site staff is unable to contact the subject/parent/legal guardian on the first 2 attempts. If the subject/parent/legal guardian cannot be contacted on a given day, during the next contact the study site staff will retrospectively collect the missed DESS, in addition to the current day's DESS, as necessary. Clinical site staff will record the responses in the subject's source information and in the CRF with the contact date and time. As noted above, all subjects will return to the clinic 3 weeks (± 7 days) after the final dose of study drug for withdrawal (DESS and the PWC) and EOS safety assessments (Visit 13E).

Subjects who discontinue from the study prior to completion will be asked to return to the clinical site and complete the Early Termination assessments within 3 days of discontinuation and complete all withdrawal period assessments (calls) and EOS visit.

After the EOS visit or upon discontinuation of study drug, all subjects will be referred for continuation of their care as determined by the investigator.

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.

Figure 1: Study Schematic



[a] There will be no break in study drug treatment between the core study and this extension study .
[b] Dasotraline will be dosed at 2 mg/day for the first week of the study (Days 1 - 7). Subjects will then be flexibly dosed (2, 4, or 6 mg/day) thereafter beginning on Day 8 based on the investigator's assessment of effectiveness and tolerability.

7.2. Rationale

7.2.1. Rationale for the Study Design

This is an open-label study to evaluate the long-term safety and effectiveness of flexibly-dosed dasotraline consistent with the intended long-term use of the compound in this population.

7.2.2. Rationale for the Dosages

Given the similarities observed in pharmacokinetics between adult and pediatric subjects, predictions from a population pharmacokinetic (PK) model of dasotraline previously established in adult subjects were evaluated against the observed single-dose pharmacokinetics in pediatric subjects enrolled in Study SEP360-105. Model predictions of the observed dasotraline single-dose pharmacokinetics in Study SEP360-105, using subjects (smaller) body sizes in the combined population PK model, corresponded well with the observed pharmacokinetics in Study SEP360-105. Thus, available dasotraline concentration data collected from pediatric subjects enrolled in Study SEP360-105 (1, 2, 4, and 8 mg cohorts, ages 6 to 17 years old) were pooled together with the previously developed population PK dataset and when the model was re-evaluated good model fit was demonstrated for all subjects encompassing a broad range of body sizes.

The dose range to be used in this study (2, 4, and 6 mg/day) was selected based on evaluation of data from a combined dasotraline population pharmacokinetic (PK) model. This analysis demonstrated that the model-based predictions for dose-exposure distributions in pediatric subjects for the doses of 2 mg/day and 4 mg/day fall within the dose-exposure distributions observed for adults following treatment with dasotraline 4 mg/day and 8 mg/day, which demonstrated clinically significant efficacy after 4 weeks of treatment in an adult ADHD population. The 6 mg/day dose was included to allow for flexibility of dosing in this long-term trial and to evaluate the safety and tolerability of this dose in the pediatric population. Dasotraline has been shown to be generally safe and well-tolerated at equivalent doses in adults.

All subjects in the current study will initially be started at 2 mg/day and then be flexibly dosed (2, 4, or 6 mg/day) thereafter.

7.2.3. Rationale for the Study Population

The subject population includes males and females ranging from 6 to 12 years of age (at time of consent/assent and at Baseline in the core study SEP360-202); 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 a primary diagnosis of ADHD (inattentive, hyperactive, or combined presentation); diagnosis was confirmed at screening for the core study using the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL).

7.2.4. Rationale for the Endpoints

The safety assessments and their timing are considered appropriate to assess the long-term safety of dasotraline, taking into account known pharmacology and adverse events based on previous studies. The symptom, functional, and quality of life assessments were selected to address the potential effectiveness of dasotraline on these parameters.

7.2.5. 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) allowance of dose adjustment throughout the study based on effectiveness and tolerability, (ii) study site

contact with subjects between the monthly study visits during the treatment period, (iii) site training on the importance of continued follow-up and on the informed consent process, ensuring subject/parent/legal guardian understand the commitment they are making, including the intent to complete the trial, and (iv) data monitoring for adherence during the study.

8. SELECTION OF SUBJECTS

Eligibility criteria will be assessed at the open-label (OL) Baseline visit (Week 6 in the core study). Assessments performed as part of the Week 6 visit in the core study do not need to be repeated.

8.1. Subject Inclusion Criteria

1. 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 complete an informed assent prior to study participation.
2. Subject and subject's parent/legal guardian are judged by the investigator to be willing and able to comply with the study procedures and visit schedules.
3. Subject has completed all required assessments for Week 6 of the core study.
4. Subject has not taken any medication other than the study drug for the purpose of controlling ADHD symptoms during the core study.
5. Subject, if female, must not be pregnant or breastfeeding.
6. Female subject:
   - must be unable to become pregnant (eg, premenarchal, surgically sterile, etc);

     -OR-
   - practice true abstinence (consistent with lifestyle) and must agree to remain abstinent from signing informed consent/assent to at least 14 days after the last dose of study drug has been taken;

     -OR-
   - is sexually active and willing to use a medically effective method of birth control (see Appendix IV, Section 23) from signing informed consent/assent to at least 14 days after the last dose of study drug has been taken.
7. Male subject must be willing to remain sexually abstinent (consistent with lifestyle) or use an effective method of birth control, (Appendix IV, Section 23), from signing informed consent/assent to at least 14 days after the last dose of study drug has been taken.
8. Any subject whose weight is < 21 kg at the OL Baseline visit should be discussed with the medical monitor prior to enrollment.
9. Subject and subject's parent/legal guardian must be able to fully comprehend the informed consent/assent form (as applicable), understand all study procedures, and be able to communicate satisfactorily with the Investigator and study coordinator.

8.2. Subject Exclusion Criteria

1. Subject is considered by the investigator to be at imminent risk of suicide, injury to self or to others, or damage to property.
2. 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 "Since Last Visit" assessment at OL Baseline.
3. Subject has a clinically significant abnormality including physical examination, vital signs, ECG, or laboratory tests that the investigator in consultation with the medical monitor considers to be inappropriate to allow participation in the study.
4. Subject has a positive urine drug screen (UDS) or breath alcohol test at OL Baseline.
5. Subject or parents/legal guardian has commitments during the study that would interfere with attending study visits.
6. Subject is at high risk of non-compliance in the investigator's opinion.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

The study medication is described in Table 5.

Table 5: Investigational Product

Attribute	Study Medication		
Product name	Dasotraline 2 mg	Dasotraline 4 mg	Dasotraline 6 mg
Dosage form	capsules	capsules	capsules
Unit dose	capsule	capsule	capsule
Route of administration	oral	oral	oral
Physical description	Swedish orange, size #4	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.

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, 4 mg, or 6 mg capsules (7 days + 3 extra days).

9.2.2. Labeling Description

All packaging for the study medications 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 number (if needed)
- Batch number
- Blank space to record visit number identifier
- Unique medication number (if needed)

9.3. Study Drug Storage

All study medication should be stored at United States Pharmacopeia (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/legal guardian will be instructed to store the study medication at room temperature.

In addition, the subject's parent/legal guardian 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 previous ADHD treatments from the subject's access.

9.4. Dispensing of Study Drug

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

The IXRS will be used to assign subject numbers that will be linked via IXRS to the subject's previous core study subject number.

Study medication blister cards will be assigned by the IXRS based on the treatment schedule determined by the investigator. The IXRS will generate instructions on which medication number to assign to a subject. Each subject will be dispensed one to four 10-day blister cards per scheduled visit, based on the expected next visit date.

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

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the study drug in a secure location and for maintaining adequate records of study 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 study drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/ contract 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 Clinical Inventory Management System (CIMS) will be used for the accountability of the supplies at the clinical site. The Investigator, or designee, will maintain the inventory for accountability within CIMS, including CTM disposition, return and availability of CTM received. The Investigator, or designee, agrees to collect and document all used and unused study medication from study subjects at appropriate study visits.

9.6. Study Drug Handling and Disposal

The Investigator or designee, on an ongoing basis, must maintain a study drug inventory record of supplied, received, dispensed, and returned study drug. Access will be provided to the Sponsor's CIMS to document study drug inventory records.

The study drug will not be dispensed for use by any person who is not a study subject under this protocol.

The Investigator or designee is required to return all used and unused study drug to the Sponsor or designee as instructed. The Investigator or designee is required to maintain copies of study drug shipping receipts, study drug accountability records, and records of return or final disposal of the study drug.

10. TREATMENT OF SUBJECTS

10.1. Study Medication

Dasotraline 2, 4, and 6 mg capsules for oral administration will be supplied for the study as described in Section 9.1.

Under supervision from the subject's parent/legal guardian, subjects will self-administer the study drug on an outpatient basis beginning on Day 1, the morning following the OL Baseline visit. All dasotraline doses will consist of 1 capsule taken orally once a day for 26 weeks (Day 1 through Day 182) at approximately the same time each morning including on the days when clinic visits occur. If morning dosing is not tolerated then dosing may be at another time of day with prior medical monitor approval; however, if there is a time of day dosing change, subjects should administer study drug at the same time of day for the remainder of the study.

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. Dose Adjustment Criteria

Dasotraline will be dosed at 2 mg/day for the first week of the study (Days 1 - 7). Subjects will then be flexibly dosed (2, 4, or 6 mg/day) thereafter beginning on Day 8 based on the investigator's assessment of effectiveness and tolerability. All changes in study drug dose will begin the morning after the visit at which the dose change decision is made and using the new package of study drug. Additional dose adjustment is allowed during the study at the discretion of the investigator; the dose may be increased or decreased by 2 mg/day, as necessary for effectiveness or tolerability reasons. Total daily dose will not exceed 6 mg/day. There is no limit on the number of dose increments or reductions during the study. A minimum of 7 days is required between dose increases. Dose decreases may be made at less than 7 day intervals for safety/tolerability reasons, at the investigator's discretion.

Subjects wishing to take study drug at an alternate time of day require investigator and medical monitor approval.

10.3. Concomitant Medications and Therapies

The following information on all medication, other than study drug, taken by or administered to the subject between OL Baseline and End of Study or at discontinuation will be recorded on the case report form (CRF):

Medication name, dose, frequency, route, start date, stop date, and indication.

10.3.1. Prohibited Medications

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

- Lithium (any lithium preparation or formulation).

- Alpha-2 adrenergic receptor agonists (including clonidine and guanfacine), modafinil, armodafinil, atomoxetine, or any stimulant class agent (methylphenidate- or amphetamine-based).
- Antidepressant medications (eg, bupropion, selective serotonin reuptake inhibitor [SSRI]/ serotonin norepinephrine reuptake inhibitor [SNRI], monoamine oxidase [MAO] blocker, tricyclic, etc) and St. John's Wort.
- Anticonvulsant medications (eg, phenytoin, carbamazepine, lamotrigine, valproic acid, etc) and antipsychotic medications.
- Pseudoephedrine-containing medications for treatment of allergies or flu-like symptoms.
- 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 (see Section 10.3.3).
- Any medications for the treatment of ADHD.
- CYP2B6 substrates or inhibitors or inducers of CYP2B6 (see Appendix II, Section 21).

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.

10.3.2. Prohibited Therapies

Subjects undergoing cognitive behavioral therapy (CBT) are excluded from entering the study. In addition, a new course of CBT specifically for ADHD is not allowed during the study.

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.

10.3.3. Permitted Medications

Use of medications not listed under prohibited medications in Section 10.3.1 are permitted during the study.

Melatonin (≤ 5 mg/day) may be administered at bedtime for insomnia, as needed. For those subjects taking melatonin, over the counter melatonin should be used; combination melatonin products are not allowed. Subjects should avoid taking these products within 8 hours prior to scheduled study assessments.

Contraception requirements are described in Appendix IV (Section 23).

10.4. 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 (ie, during the absorption process).

10.5. Cautions

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

10.6. Dietary Guidelines

Study drug may be taken without regard for food.

10.7. Treatment Compliance

Compliance with study drug will be monitored closely and determined at each visit during treatment. Subjects and their parents/legal guardians will be instructed to bring all unused study drug with them to each 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 subject and their parent/legal guardian, and at the investigator's discretion may result in termination of the subject from the study. All subjects and their parents/legal guardians 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.

10.8. Treatment Assignment and Blinding

10.8.1. Treatment Assignment

This is a single-arm, open-label study. All subjects will receive dasotraline flexibly dosed at 2, 4, or 6 mg/day.

10.8.2. Blinding

Blinding of study treatment is not applicable; this is an open-label study.

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.

Training, as appropriate, will be provided for study site staff that did not participate in the core study and will be administering any of the effectiveness and safety assessments in this study. In an effort to improve the consistency of subject assessment across sites, an independent rater qualification service, Bracket, will provide training on the ADHD-RS-IV HV, Conners 3-P, CGI-S, CSHQ, Tanner staging, WFIRS-P, DESS, and PWC. In an effort to improve rater consistency and precision, Bracket, in collaboration with the sponsor, will develop a credential and experience survey to identify raters with appropriate experience. The sponsor has final discretion regarding allowing raters to participate in the study.

11.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics obtained for the core study including date of birth, sex, ethnicity, race, weight, height, BMI, physical and brief neurological examination results, and medical and psychiatric history will be carried over for this study and duplicate assessments will not be conducted.

11.2. Efficacy Assessments

11.2.1. Efficacy Scales

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

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.

Clinical Global Impression–Severity of Illness (CGI-S)

Following a clinical interview, the CGI-S can be completed in 1 – 2 minutes. The CGI-S modified (Guy-1976) asks the clinician one question: “Considering your total clinical experience with this population, how mentally ill is the subject at this time?” The clinician’s answer is rated on the following 7 point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill subjects.

This rating is based upon observed and reported ADHD symptoms, behavior, and function in the past 7 days. Clearly, symptoms and behavior can fluctuate over a week; the score should reflect the average severity level across the 7 days.

The Conners 3rd Edition Parent (Conners 3-P)

The Conners 3–P assesses behaviors and other concerns in children between the ages of 6 and 18, inclusive. The full-length version of the Conners 3–P will be used. The full-length version provides a thorough assessment of ADHD and addresses comorbid disorders such as oppositional defiant disorder (ODD) and conduct disorder. Responses to the Conners 3-P will be used to calculate the total score and subscale scores (Oppositional, Cognitive problems, Hyperactivity, and ADHD Index).

At each timepoint the review will include the past month.

Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P)

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

11.3. 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 during study conduct.

11.3.1. Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 12, Safety Reporting.

AEs and SAEs will be monitored throughout the study at all visits including telephone assessments.

11.3.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Appendix III (Section 22). See Appendix V (Section 24) for estimated blood volumes to be collected from the subject during the course of the study.

Blood and urine samples will be collected for clinical laboratory tests. Use of a dermal anesthetic to prevent pain associated with blood sampling is permitted. All clinical laboratory tests will be performed centrally. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Laboratory Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories must be College of American

Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

11.3.3. Physical and Neurological Examinations

Clinically significant physical and neurological examination findings, as judged by the investigator, will be recorded as AEs.

Body weight while wearing street clothes and without shoes will be recorded in kilograms (kg). Height without shoes will be measured by stadiometer and recorded in centimeters (cm).

11.3.4. Vital Signs

Respiratory rate and oral 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.

11.3.5. ECGs

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 laboratory according to established quality assurance procedures for inter/intra reader variability. Refer to Appendix I (Section 20) for additional information.

Standard 12 lead ECG parameters heart rate (HR), PR interval, RR interval, QT interval, QTcB and QTcF intervals, and QRS duration will be assessed.

11.3.6. 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.

For all 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.

Children's Sleep Habits Questionnaire (CSHQ)

The CSHQ is a retrospective, 45-item parent questionnaire that is used to examine sleep behavior in young children (Owens-2000). The CSHQ includes items relating to a number of key sleep domains that encompass the major presenting clinical sleep complaints in this age group: bedtime behavior and sleep onset; sleep duration; anxiety around sleep; behavior occurring during sleep and night wakings; sleep-disordered breathing; parasomnias; and morning waking/daytime sleepiness. Parents are asked to recall sleep behaviors occurring over a "typical" recent week. Items are rated on a 3-point scale: "usually" if the sleep behavior occurred 5 to 7 times/week; "sometimes" for 2 to 4 times/week; and "rarely" for 0 to 1 time/week. Some items were reversed in order to consistently make a higher score indicative of more disturbed sleep. For the purposes of further psychometric evaluation analysis, some of the CSHQ items were eliminated as redundant or ambiguous, and the remaining 35 numbered items on the scale were conceptually grouped into 8 subscale scores reflecting the following sleep domains: (1) Bedtime Resistance; (2) Sleep Onset Delay; (3) Sleep Duration; (4) Sleep Anxiety; (5) Night Wakings; (6) Parasomnias; (7) Sleep-Disordered Breathing; (8) Daytime Sleepiness. Responses to the CSHQ will be used to calculate the total score and 8 domain scores.

Tanner Staging

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

Discontinuation--Emergent Signs and Symptoms (DESS) Scale

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

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

Physician Withdrawal Checklist (PWC)

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

11.4. Study Visits and Assessments

11.4.1. Open-label Baseline: Visit 1E (Day 0)

Subjects will be evaluated at the Open-label Baseline Visit to determine their eligibility to enroll in the study. The following study-related procedures will be performed at Open-label Baseline in the following order:

- Obtain informed consent/assent
- Review inclusion/exclusion criteria
- Dispense study drug

The following study-related procedures will be carried over from the core study Week 6 visit and do not need to be performed for the Open-label Baseline visit:

- Medical and psychiatric histories
- Physical and neurological examinations
- Concomitant medications
- Vital signs, height, weight, and BMI
- AEs
- ECG
- Tanner Staging
- C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- WFIRS-P
- Clinical laboratories (hematology, chemistry, lipid panel, thyroid panel, sex hormone tests, urinalysis), UDS, and serum pregnancy test for females of child bearing potential
- Breath alcohol test

11.4.2. Visit 2E: Week 1 (Day 7 ± 3)

- Record concomitant medications
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Perform study drug accountability
- Dispense study drug

11.4.3. Visit 3E: Week 2 (Day 14 ± 3)

- Record concomitant medications
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Collect sample for UDS
- Perform study drug accountability
- Dispense study drug

11.4.4. Visit 4E: Week 4 (Day 28 ± 3)

- Record concomitant medications
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Perform study drug accountability
- Dispense study drug

11.4.5. Visit 5E: Week 6 (Day 42 ± 3)

- Record concomitant medications
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Collect sample for UDS and urine pregnancy test for females of childbearing potential
- Perform study drug accountability
- Dispense study drug

At the approximate midpoint between Visit 5E (Week 6) and Visit 6E (Week 10), contact the subject to evaluate safety (See Section 11.4.12).

11.4.6. Visit 6E: Week 10 (Day 70 ± 3)

- Record concomitant medications
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Collect sample for UDS and urine pregnancy test for females of childbearing potential
- Perform study drug accountability
- Dispense study drug

At the approximate midpoint between Visit 6E (Week 10) and Visit 7E (Week 14), contact the subject to evaluate safety (See Section 11.4.12).

11.4.7. Visit 7E: Week 14 (Day 98 ± 3)

Subjects should be fasted (no food or drink except water at least 8 hours prior to blood draws for the lipid panel). Blood samples should be drawn in the morning followed by a snack or meal.

- Record concomitant medications
- Perform physical and neurological examination
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Parent/legal guardian completes WFIRS-P
- Collect sample for clinical laboratories (hematology, chemistry, thyroid, lipid panel, thyroid function panel, urinalysis), UDS, urine pregnancy test for females of child bearing potential, sex hormone tests
- Perform breath alcohol test
- Perform study drug accountability
- Dispense study drug

At the approximate midpoint between Visit 7E (Week 14) and Visit 8E (Week 18), contact the subject to evaluate safety (See Section 11.4.12).

11.4.8. Visit 8E: Week 18 (Day 126 ± 3)

- Record concomitant medications
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Collect sample for UDS, and urine pregnancy test for females of childbearing potential
- Perform study drug accountability
- Dispense study drug

At the approximate midpoint between Visit 8E (Week 18) and Visit 9E (Week 22), contact the subject to evaluate safety (See Section 11.4.12).

11.4.9. Visit 9E: Week 22 (Day 154 ± 3)

- Record concomitant medications
- Collect vital signs, height, weight, and BMI

- Perform ECG
- Record AEs
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ
- Collect sample for UDS and urine pregnancy test for females of childbearing potential
- Perform study drug accountability
- Dispense study drug

At the approximate midpoint between Visit 9E (Week 22) and Visit 10E (Week 26), contact the subject to evaluate safety (See Section 11.4.12).

11.4.10. Visit 10E: Week 26 (Day 182 ± 3) / Early Termination

Subjects should be fasted (no food or drink except water at least 8 hours prior to blood draws for the lipid panel). Blood samples should be drawn in the morning followed by a snack or meal.

- Record concomitant medications
- Perform physical and neurological examination
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Perform Tanner Staging
- Administer C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ, DESS, PWC
- Parent/legal guardian completes WFIRS-P
- Collect sample for clinical laboratories (hematology, chemistry, thyroid function panel, lipid panel, urinalysis), UDS, urine pregnancy test for females of childbearing potential, sex hormone tests
- Perform study drug accountability

11.4.11. Withdrawal Period

11.4.11.1. Visit 11E /Telephone Contact: Week 27 (Day 189 ± 3)

- Administer DESS

Clinical site staff may call up to 3 times per day if the clinical site staff are unable to contact the subject/parent/legal guardian on the first 2 attempts. If the subject/parent/legal guardian cannot be contacted on a given day, during the next contact the study site staff will retrospectively collect the DESS from the missed day and the current day, as necessary.

11.4.11.2. Visit 12E /Telephone Contact: Week 28 (Day 196 ± 3)

- Administer DESS

Clinical site staff may call up to 3 times per day if the clinical site staff are unable to contact the subject/parent/legal guardian on the first 2 attempts. If the subject/parent/legal guardian cannot be contacted on a given day, during the next contact the study site staff will retrospectively collect the DESS from the missed day and the current day, as necessary.

11.4.11.3. Visit 13E / End of Study: Week 29 (Day 203 ± 7)

Subjects should be fasted (no food or drink except water at least 8 hours prior to blood draws for the lipid panel). Blood samples should be drawn in the morning followed by a snack or meal.

- Record concomitant medications
- Perform physical and neurological examination
- Collect vital signs, height, weight, and BMI
- Perform ECG
- Record AEs
- Administer C-SSRS, DESS, PWC
- Collect sample for clinical laboratories (hematology, chemistry, thyroid function panel, lipid panel, urinalysis), UDS, serum pregnancy test for females of childbearing potential, sex hormone tests
- Perform breath alcohol test

11.4.12. Between Visit Contacts

A member of the study site staff will contact the subject/parent/legal guardian via telephone, text, or email between monthly visits during the treatment period according to the timeline in Table 6. These contacts will be used to monitor for clinical symptoms and adverse events, as well as to remind subjects about adherence to study drug administration and upcoming visits. The date and time of these contacts will be documented in the CRF.

Table 6: Between Visit Contact Timeline

Study Visit Timing[a]
Approximate midpoint between Visits 5E and 6E (ie, 14 ± 2 days after visit)
Approximate midpoint between Visits 6E and 7E (ie, 14 ± 2 days after visit)
Approximate midpoint between Visits 7E and 8E (ie, 14 ± 2 days after visit)
Approximate midpoint between Visits 8E and 9E (ie, 14 ± 2 days after visit)
Approximate midpoint between Visits 9E and 10E (ie, 14 ± 2 days after visit)

[a] The exact timing of each contact will be determined based on the actual timing of the scheduled visits.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a study subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment.

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 the time the informed consent is obtained 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 (ie, a patient is at immediate risk of death at the time of the event, not an event where occurrence in a more severe form might have caused death).
- 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 (eg, elective surgery) that was scheduled before the study entry, ie, 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.

12.2. Objective Findings

Clinically significant abnormal objective findings (eg, 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 (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, 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 clinical site. 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 the Screening phase is indicated as clinically significant and is not covered by the eligibility 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 End of Study 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 Adverse Events

All AEs must be collected and recorded in the subject's study records/source documents, in accordance with the Investigator's normal clinical practice, and on the CRF from the time the informed consent/assent is signed through the last study visit or discontinuation. All AEs will be followed up 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 Reduced.**
- **Dose Increased.**
- **Dose Not Changed.**
- **Not Applicable.**

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 site staff becomes aware of SAE that occurs in a study subject from the time that informed consent/assent is signed 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 occurring from the time of informed consent to through 14 days following last dose of the study medication must be recorded on the CRF and the data recorded should match 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 telephone 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 site staff becoming aware of the event. The SAE report form must be signed by the Investigator or appropriate designee. The Sponsor provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study sites 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) or Independent Ethics Committee (IEC) by the Principal Investigator or the appropriate person at the site.

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent/assent is signed 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 discontinue 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 research site and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the 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 site staff becoming aware of the pregnancy. The Sponsor provides the Pregnancy Event Form.

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 Monitoring Committee/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 their 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
- Lost to follow-up
- Pregnancy
- Withdrawal by subject
- Noncompliance
- Protocol violation
- Other

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 (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study treatment.

The reason for discontinuation will be recorded on the appropriate CRF.

Subjects who prematurely terminate the study participation will not be replaced.

Subjects who discontinue study drug prior to completion will be asked to return to the site and complete the Early Termination visit assessments (Visit 10E/ET; Section 11.4.10) within 3 days of study drug discontinuation and complete all withdrawal period assessments (calls) and the EOS visit (Visit 13E; Section 11.4.11.3).

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time while ensuring that early termination does not compromise subjects' safety or well-being. In particular, a site that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the site 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 for a final study assessment 3 days after their last dose of study drug and provided with access to standard care.

15. STATISTICS

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

All statistical summaries will be presented by treatment group from the double-blind core study as well as all subjects in the extension study.

Changes from baseline in safety and effectiveness endpoints will be calculated from both the double-blind (DB) baseline in the core study and the open-label (OL) baseline in the extension study, which is the Week 6 endpoint in the core study for most measures. No statistical inference will be performed for treatment comparison as this is a single arm, open-label, extension study.

15.1. Sample Size Determination

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

15.2. Analysis Populations

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

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

15.3. Data Analysis

15.3.1. Subject Disposition

Subject disposition will be summarized for all enrolled subjects. Subjects who completed the study and discontinued early from the study will be summarized. The primary reason for discontinuation from the study will also be presented.

15.3.2. Drug Exposure and Compliance

A descriptive summary will be performed to summarize exposure to study drug. Treatment compliance will be determined and summarized descriptively.

15.3.3. Important Protocol Deviations

Protocol deviations will be collected during monitoring visits. Protocol deviations will be placed into the following categories: concomitant medications, dosing, enrollment criteria, laboratory, non-compliance, visit schedule, visit/procedure requirement, and others. Protocol deviations will be reviewed and determination of importance will be made prior to DBL.

A summary of protocol deviations will be provided as number (%) of subjects with at least one protocol deviation and number (%) of subjects by category.

15.3.4. Demographic and Baseline Characteristics

Demographics (sex, race, ethnicity, age [years], age group, baseline weight [kg], height [cm], and BMI [kg/m^2]) will be summarized for the Safety population. Sex, race, age group, and ethnicity will be summarized using summary statistics for categorical variables (frequencies and percentages). Age, baseline height, baseline weight, and baseline BMI will be summarized using summary statistics for continuous variables (number of subjects, mean, standard deviation, median, minimum and maximum values).

15.3.5. Effectiveness Analysis

This is a single arm, open-label, extension study therefore no inferential statistics will be performed for any the effectiveness variables.

15.3.5.1. Effectiveness Endpoint Analyses

For effectiveness evaluations, descriptive statistics of observed value and change from both DB and OL baselines in the following endpoints will be summarized by visit.

- Change in ADHD-RS-IV HV total score.
- Change in CGI-S score.
- Change in the ADHD-RS-IV HV inattentiveness and hyperactivity-impulsivity subscale scores.
- Change in Conners 3-P score and subscale scores (Oppositional, Cognitive problems, Hyperactivity, and ADHD Index).
- Change in WFIRS-P total score and 6 domain scores (family, learning and school, life skills, child's self-concept, social activities, and risky activities).

15.3.5.2. Subgroup Analysis

Subgroup summary in change from baseline in ADHD-RS-IV HV total score will be provided by sex, race (eg, White, Black or African American, Asian, and Other) and age group in the ITT Population.

15.3.6. Safety Analysis

15.3.6.1. Adverse Events

The summary of AEs and SAEs will be limited to TEAEs. A TEAE is any AE (or SAE) occurring after the first dose of study drug and before the end of the 2-week study follow-up period. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 or higher.

The TEAEs will be summarized by system organ class (SOC) and preferred term (PT) by presenting the number and percentage of subjects with each TEAE. The TEAE summary will be produced for the following categories:

- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT

- TEAEs leading to discontinuation by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- Treatment-related TEAEs by SOC and PT
- Treatment-related serious TEAEs by SOC and PT
- TEAE leading to death by SOC and PT

A subject with multiple adverse events during the study will only be counted only once in a category per SOC and PT. The same subject may appear in different categories per SOC and PT. If a subject has the same AE on multiple occasions, the highest severity (severe, moderate, mild) recorded for the event will be presented and the highest drug relationship (Unrelated, Unlikely to be Related, Possibly Related, Probably Related, Definitely Related), reclassified into Related (Possibly Related, Probably Related, Related) or Not Related (Unrelated and Unlikely to be Related), will be presented on the respective tables. Percentages are based on the number of subjects in the Safety population.

15.3.6.2. Clinical Laboratory Assessments

The laboratory results collected in conventional units will be converted to SI units for the summaries.

Clinical laboratory test results (hematology, chemistry, lipid panel, thyroid function panel, sex hormones, and urinalysis) and their changes from baseline will be summarized by visit using descriptive statistics. Shift tables comparing laboratory test results from OL baseline to end of study will be presented. In addition, the markedly abnormal post-baseline laboratory results will be summarized for certain laboratory tests.

15.3.6.3. Centrally-read ECG

Actual values and changes from baseline in ECG parameters (QTc, Bazetts corrected QTcB, Fridericia corrected QTcF, heart rate, PR interval, QRS interval, and RR interval) will be descriptively summarized by visit. The incidence of subjects with clinically abnormal QTc intervals and clinically significant changes in QTc intervals will also be summarized.

15.3.6.4. Vital Signs

Vital signs (blood pressure, pulse rate, height, weight, BMI, and respiration rate) will be monitored at every visit. Each vital sign parameter will be summarized at each visit for the observed value and change from baseline. In addition, the markedly abnormal post-baseline vital signs results will also be summarized for subjects with at least one markedly abnormal value during the 26-week treatment period. A shift table will be presented comparing shifts from the baseline visit to end of study. The number and percentage of subjects who experienced orthostatic hypotension at each time point will be summarized.

15.3.6.5. Neurological Examination

Neurological examination assessments will be summarized using summary statistics for categorical variables (normal/abnormal) by visit.

15.3.6.6. Tanner Staging

Descriptive statistics will be provided by visit based on observed values and changes from baselines in Tanner Staging.

15.3.6.7. Breath Alcohol Test

Breath alcohol examination assessments will be summarized using summary statistics for categorical variables (negative/positive) by visit.

15.3.6.8. Prior and Concomitant Medications

All medications will be coded using the World Health Organization drug dictionary (WHODRUG) version Q32014 (September 1st, 2014 release) or higher.

The prior medications will include medications started prior to the first dose date of study drug. The concomitant medications will include medications started on or after the first dose date of study drug.

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

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

The frequency and percentage by visit will be summarized for all C-SSRS responses. Frequency and severity of suicidality using the C-SSRS will be summarized using a shift table to examine changes in C-SSRS Scores from baseline compared to the worst (highest) category during the 26-week treatment period by visit.

15.3.6.10. Children's Sleep Habits Questionnaire (CSHQ)

Changes from baseline in CSHQ total score and 8 subscale scores (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness) will be summarized descriptively.

15.3.6.11. Physician Withdrawal Checklist (PWC), and Discontinuation-Emergent Signs and Symptoms (DESS) Scale

The PWC will be summarized using descriptive statistics by visit for the total score. The frequency and percentage of subjects with a 'Present' response will be summarized for each of the 20 PWC items. In addition, responses of 'moderate' or 'severe' will be summarized separately by each visit. The DESS score from the last day of treatment and during the 3-week follow-up period will be summarized, as appropriate.

15.3.6.12. Subgroup Analyses

Subgroup summary analysis will be conducted on overall TEAEs to examine sex, race (eg, White, Black or African American, Asian, and Other), and age group in the Safety population.

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

16.1. Data Collection/Electronic Data Capture (EDC)

The results from baseline and data collected during the study (except clinical laboratory test results, electrocardiogram results, and IXRS data) will be recorded in the subject's electronic CRF. The C-SSRS, CGI-S, ADHD-RS-IV HV, Conners 3-P, CSHQ, WFIRS-P, DESS, and PWC will be completed on paper and then entered into the electronic data capture (EDC) system. The study sites will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 Code of Federal Regulations (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/assent	NA
Inclusion/Exclusion criteria	A
Dispense study drug	A, D
Study drug accountability	A, E
Between visit contact	A
Medical and Psychiatric History	A
Concomitant medication review	A
Physical examination	A
Neurological examination	A
Height (measured by stadiometer)	A
Weight (including body mass index)	A
Vital signs	A
Electrocardiogram (ECG)	C
Adverse event monitoring	A
Tanner Staging	A
Columbia Suicide Severity Rating Scale (C-SSRS) Children's Assessment	A
Clinical Global Impression – Severity (CGI-S)	A
ADHD Rating Scale Version IV - Home Version (modified for investigator administration) (ADHD-RS-IV HV)	A
The Conners 3rd Edition Parent (Conners 3-P)	A
Children's Sleep Habits Questionnaire (CSHQ)	A
Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P)	A
Physician Withdrawal Checklist (PWC)	A
Discontinuation-Emergent Signs and Symptoms (DESS) Scale	A
Hematology/Chemistry	B
Thyroid panel	B
Lipid panel	B
Sex hormone tests	B
Serum β-hCG (in females)	B
Urinalysis	B
Urine drug screen	A
Urine β-hCG (in females)	A
Breath alcohol test	A
Statistical Analysis	SAS®, version 9.1.3 or higher

A = EDC (Medidata Rave); B = LIMS; C = Core Lab Over-read; D = IXRS; E = CIMS.
Abbreviations: β-hCG = beta- human chorionic gonadotropin; CIMS = Clinical Inventory Management System; EDC = electronic data capture (Medidata Rave®); IXRS = interactive recognition system; LIMS = laboratory information management system; NA = not applicable.

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/parent/legal guardian granting consent 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/IEC 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 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/Independent Ethics Committee

Documented approval for conducting the study from appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be obtained for all participating 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/IEC approval must be obtained and also forwarded to the Sponsor. The IRB/IEC must supply the Sponsor a list of the IRB/IEC membership, and a statement to confirm that the IRB/IEC is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB/IEC approval or favorable opinion of the protocol, informed consent/assent 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/IEC chairman or designee identify the IRB/IEC 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/IEC complies with the requirements in 21 CFR Part 56 for a study conducted under a US IND or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable

regulations, at intervals not to exceed one year or as otherwise specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC 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 and assent forms will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. The Sponsor/CRO may provide a template informed consent/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/IEC approval. The Sponsor/CRO may submit informed consent/assent forms to a central IRB/IEC for review and approval or favorable opinion contingent upon the Investigator's permission and review.

Before recruitment and enrollment, each prospective subject and at least one parent/legal guardian will be given a full explanation of the study, allowed to read the approved informed consent/assent forms 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/assent, as appropriate, to participate in the study by signing the informed consent/assent form unless otherwise instructed by the IRB. As part of the consent/assent process, each prospective subject/parent/legal guardian must consent/assent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC 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 will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent/assent form to each subject/parent/legal guardian, and will record the date of the informed consent 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 must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent/assent form 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/assent 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 and initials 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/IEC. 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/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC 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/IEC immediately/within 5 business days of the occurrence, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the site must arrange for retention of study records at the site 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 site 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, 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. INVESTIGATOR APPROVAL

I have read the protocol, SEP360-310, Version 3.00, "An Open-label, Flexibly-dosed, 26-Week Extension Safety Study of Dasotraline in Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD)", 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: _____

19. REFERENCES

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20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

ECG equipment and supplies will be provided by the 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 site 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 included.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested for at least 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 site 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 site.

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. 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		

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22. APPENDIX III. CLINICAL LABORATORY TESTS

The following clinical laboratory tests are to be performed:

Clinical Safety Panel

HEMATOLOGY:

Hemoglobin, Hematocrit, Platelet Count, RBC Count, WBC - Total Count, WBC Differential reported as % and absolute value to include basophils, eosinophils, lymphocytes, monocytes, neutrophils

BLOOD CHEMISTRIES:

Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO_3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

URINALYSIS:

Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

THYROID PANEL:

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

LIPID PANEL

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

SEX HORMONES:

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

URINE DRUG SCREENING:

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

OTHER TESTS:

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

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the 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. ACCEPTABLE CONTRACEPTIVE PROCEDURES DURING THE STUDY

Female Subjects

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

a. Non-childbearing potential (ie, 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 baseline and agrees to satisfy one of the following requirements:

   - Practice true abstinence (consistent with lifestyle) from signing informed assent/consent to at least 14 days after the last dose of study drug; or,
   - Use of medically effective method of birth control from signing informed assent/consent 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

1. 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.

24. APPENDIX V. TOTAL BLOOD VOLUMES

An estimated 37.5 mL of blood will be collected for study assessments from each subject during the study as shown in Table 8.

Table 8: Blood Collection Volumes (mL)

Visit	1E	2E	3E	4E	5E	6E	7E	8E	9E	10E /ET	11E	12E	13E /EOS	
Week	**Baseline**	**1**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**27**	**28**	**29**	
Day (±3[c])	**0**	**7**	**14**	**28**	**42**	**70**	**98**	**126**	**154**	**182**	**189**	**196**	**203 (±7)**	
Lab test														**Total**
Hematology	CO						2			2			2	6
Chemistry	CO						8.5			8.5			8.5	25.5
Thyroid Panel[b]	CO													
Lipid Panel[b]	CO													
Sex Hormone Tests	CO						2			2			2	6
Serum pregnancy (Females)[a,b]	CO													
TOTAL	0	0	0	0	0	0	12.5	0	0	12.5			12.5	37.5

Abbreviations: CO = Carried over from core study (no additional blood drawn; 0 mL), EOS = End of Study; ET = Early Termination = Visit.

[a] ≥ 8 years of age.

[b] Included in serum chemistry sample.

[c] Unless otherwise specified.