



**PROTOCOL: SPD489-347**

**TITLE:** A Phase 3, Randomized, Double-blind, Multicenter, Parallel-group, Placebo-controlled, Fixed-dose Safety and Efficacy Study of SPD489 Compared with Placebo in Preschool Children Aged 4-5 Years with Attention-deficit/Hyperactivity Disorder

**DRUG:** SPD489, Lisdexamfetamine dimesylate

**IND:** 67,482

**EUDRACT NO.:** Non-EUDRACT

**SPONSOR:** Shire Development LLC and International Affiliates  
300 Shire Way, Lexington, MA 02421

**PRINCIPAL/  
COORDINATING  
INVESTIGATOR:** [REDACTED], MD

**PROTOCOL  
HISTORY:** Amendment 3: 04 Aug 2017  
Amendment 2: 05 Jun 2017  
Amendment 1: 23 Feb 2017  
Original Protocol: 01 Aug 2016

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### PROTOCOL SIGNATURE PAGE

#### Sponsor's (Shire) Approval

Signature: [REDACTED]	Date: 04 Aug 2017
[REDACTED] MD	

#### Investigator's Acknowledgement

I have read this protocol for Shire Study SPD489-347.

**Title:** A Phase 3, Randomized, Double-blind, Multicenter, Parallel-group, Placebo-controlled, Fixed-dose Safety, and Efficacy Study of SPD489 Compared with Placebo in Preschool Children Aged 4-5 Years with Attention-deficit/Hyperactivity Disorder

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____
	_____

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

### SUMMARY OF CHANGES FROM AMENDMENT 2

The changes below were made to Amendment 2. In addition, throughout the protocol, general corrections were done.

The following table provides a summary list of changes that were included in Protocol Amendment 3:

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
3	04 Aug 17	Global
Section		Description of Change
<a href="#">Signature page</a>		Global Clinical Development Lead updated
<a href="#">Table 1</a>		Minor updates made to Schedule of Assessments for clarity.
<a href="#">Table 1, Section 7.2.4.10</a>		Updated suitability of the subject to remain in the study, specifically to ask about appetite level during each AE assessment at each study visit (except for Visit 6/ET) starting with the baseline visit (Visit 0).

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[REDACTED]

or

[REDACTED]

**For protocol- or safety-related issues during normal business hours 9:00 AM to 5:00 PM Eastern Standard Time, the investigator must contact the PPD Medical Monitor:**

[REDACTED], MD, MPH

Phone: [REDACTED]

Fax: [REDACTED]

Mobile: [REDACTED] (callers will be transferred to the medical monitor's cell phone)

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[REDACTED]

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## ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS-IV	Attention-deficit/Hyperactivity Disorder Rating Scale-IV
ADHD-RS-IV Preschool Version	Attention-deficit/Hyperactivity Disorder Rating Scale-IV Preschool Version
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
BMI	body mass index
bpm	beats per minute
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impressions – Global Improvement
CGI-S	Clinical Global Impressions – Severity of Illness
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSHQ	Children’s Sleep Habits Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
<i>d</i> -amphetamine	dextroamphetamine
DBP	diastolic blood pressure
DMC	data monitoring committee
DRAS	Dose Response Analysis Set
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision
EC	ethics committee
ECG	electrocardiogram
EOS	end of study
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator’s brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
IRT	interactive response technology

IWRS	interactive web response system
K-SADS-PL	Kiddie–Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version–Diagnostic Interview
LAR	legally authorized representative
MAOI	monoamine oxidase inhibitor
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MED	minimum effective dose
MMRM	mixed-effects model for repeated measures
PAPA	Preschool Age Psychiatric Assessment
PK	pharmacokinetic
RBC	red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SAP	statistical analysis plan
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
US	United States
WBC	white blood cell

## STUDY SYNOPSIS

<b>Protocol number:</b> SPD489-347	<b>Drug:</b> Lisdexamfetamine dimesylate
<b>Title of the study:</b> A Phase 3, Randomized, Double-blind, Multicenter, Parallel-group, Placebo-controlled, Fixed-dose Safety and Efficacy Study of SPD489 Compared with Placebo in Preschool Children Aged 4-5 Years with Attention-deficit/Hyperactivity Disorder	
<b>Number of Subjects (total and for each treatment arm):</b> <p>Approximately 245 subjects will be screened to randomize approximately 195 subjects in a 5:5:5:5:6 ratio to SPD489 5, 10, 20, 30 mg or placebo to achieve 156 completers for the study (30 in each active treatment group and 36 in the placebo group) and 85% power for the primary efficacy analysis. The sample size planned at study initiation is estimated based on the primary comparison of the change from baseline in the total score on the ADHD-RS-IV Preschool Version between those who received SPD489 10, 20, 30 mg pooled vs. those randomized to placebo, using a group sequential design with 1 interim analysis, using the Lan-DeMets alpha spending function with O'Brien-Fleming boundary for the primary efficacy endpoint. Assumptions for the calculation include the true mean difference of 8.4 with the common standard deviation of 14 for the primary efficacy endpoint, for an effect size of 0.6, and a dropout rate of 20%.</p> <p>A blinded sample size re-estimation is planned to ensure sufficient study power to detect a clinically meaningful drug effect for the primary efficacy endpoint. This re-estimation will be performed after approximately 75% of the 195 randomized subjects have either completed or discontinued from the study. The proposed blinded sample size re-estimation will only be conducted if the study does not meet the primary efficacy criterion at the interim analysis, when approximately 60% of randomized subjects having completed or discontinued from the study. In this case, cumulative primary efficacy data will be used to estimate a pooled common standard deviation (SD) to ensure that the variability hypothesized at the design stage (SD = 14) is not underestimated. Together with the assumed treatment difference of 8.4, the final total number of subjects to be enrolled will be calculated using the re-estimated pooled SD. If the re-estimated pooled common SD is larger than 14, the sample size will be increased. Otherwise, the sample size will remain the same. The total number of planned completers could remain at 156, or could potentially be as high as 218, which corresponds to the 97.5% percentile of the distribution of the estimator on the assumed true common standard deviation of 14. Note that the total of 218 completers is not considered a cap. As the final sample size is data driven, a higher number, though unlikely, is possible.</p> <p>The dose-response relationship will be measured by the ADHD-RS-IV Preschool Version Total Score change from baseline. Assuming the maximum difference in change from baseline in ADHD-RS-IV Preschool Version Total Score between 0 mg (placebo) and SPD489 (5, 10, 20 or 30 mg) is 13.0 points, and has a standard deviation of 14 for the change, then in order to detect a plausible dose-response curve at 85% power and a significance level of 0.05 (2-sided) using MCP-Mod with equal allocation to the treatment groups, it is necessary to have 18 completers for each arm. Assuming a 20% dropout rate, a total of 24 subjects for each treatment group are required to be randomized. Therefore, the overall sample size of the study will be sufficient for dose-response analysis.</p> <p>Approximately 25% of the subjects enrolled will be female.</p>	
<b>Investigator(s):</b> Multicenter, ██████████, MD (Lead PI)	
<b>Site(s) and Region(s):</b> Up to 60 sites in North America	
<b>Study period (planned):</b> 2017-2019	<b>Clinical phase:</b> 3

**Objectives:**

**Primary:** To evaluate the efficacy of SPD489 compared to placebo in preschool children (4-5 years of age inclusive at the time of consent) with Attention-deficit/Hyperactivity Disorder (ADHD). The primary measure of efficacy will be the clinician-administered ADHD Rating Scale Preschool Version (ADHD-RS-IV Preschool Version) Total Score.

**Secondary:**

- **Key Secondary:** To evaluate the efficacy of SPD489 compared to placebo, using a global clinical measure of improvement, the Clinical Global Impression- Global Improvement (CGI-I) Scale.
- **Secondary:**
  - To evaluate the dose-response relationship in preschool children with ADHD, using the ADHD-RS Preschool Version Total Score.
  - To evaluate the safety and tolerability of SPD489 based on the occurrence of treatment-emergent adverse events (TEAEs), specific evaluation of vital signs (systolic and diastolic blood pressure and pulse), height, weight, and body mass index, clinical laboratory evaluations, electrocardiogram (ECG) results, sleep assessment, and the Columbia Suicide Rating Scale (C-SSRS).

**Rationale:**

Based on IMS Health data and discussion at the Food and Drug Administration (FDA) Pediatric Advisory Committee in September 2012, it has been noted that there is off-label use of SPD489 in children under 5 years old (4%, or approximately 100,000 patients between February 2007 and March 2012). The lack of controlled data regarding the safety and efficacy of SPD489 in the preschool ADHD population, in concert with the prevalence of off-label prescribing of SPD489 supports the need for SPD489 studies in the preschool ADHD population. Importantly, it is not known if the therapeutic effects of stimulant medications in school age children with ADHD can be extrapolated to preschool children with ADHD. There are some indications that the effect size may be reduced (Greenhill 2006). There may also be differences in the safety and pharmacokinetic profiles (Wigal 2007; Wigal 2006).

Generating controlled data in this population will provide practicing physicians with information on the safety and efficacy profiles of SPD489 in preschool children with ADHD.

**Investigational product, dose, and mode of administration:**

The sponsor will provide SPD489 as 5, 10, 20, and 30 mg strength capsules. The sponsor will also provide placebo, which will appear identical to the investigational product.

All subjects will be instructed to take 1 capsule daily throughout the study at approximately 7:00AM. SPD489 will be administered by means of the capsule being swallowed whole or opened, the entire contents of the capsule mixed with orange juice, water, or yogurt and the mixture administered to the subject. The subject must ingest the entire amount of the mixture immediately within 3 minutes. The empty gelatinous capsule will be discarded.

**Methodology:**

This study is a Phase 3 randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy of SPD489 compared to placebo in preschool children (4-5 years of age inclusive at the time of consent) with ADHD.

The study will have 4 periods:

- (1) Screening and Washout 28 days
- (2) Fixed-dose titration 3 weeks
- (3) Dose-maintenance 3 weeks
- (4) Safety Follow-up- 7 days

Subjects will be required to visit the site about 8 times over a 10-week period. The Schedule of Assessments (Table 1) details all procedures to be completed at each visit and should serve as the primary section regarding visit-specific study procedures.

### Screening Procedures

Subjects will be screened at Visit -1 to establish eligibility for study participation. Screening procedures may take place across multiple days to allow enough time to complete all procedures and to confirm the subject's initial eligibility.

Table 1 details all procedures to be completed at the screening visit (Visit -1). Additional clarification on the procedures performed during the screening visit (Visit -1) is provided below.

- Eligibility will be established per inclusion and exclusion criteria, including documentation of any prior non-pharmacological treatment, and specified ADHD and Clinical Global Impressions – Severity of Illness (CGI-S) severity criteria. Areas of impairment will be recorded for all subjects for assessing the severity of the subject's condition.
- All AEs occurring after signature of informed consent must be recorded in the source documents and case report form (CRF).
- Twelve-lead ECG will be performed after approximately 5 minutes of rest. The investigator will perform the initial interpretation of the ECG immediately after collection to ensure the safety of each subject. The ECG tracing will be sent to the central reader for analysis. Upon review of the report from the central reader, the investigator will re-evaluate the clinical significance of the ECG in light of other safety data for the subject. If abnormal and significant results are observed following assessment by the central reader, the investigator, in consultation with the appointed contract research organization (CRO) medical monitor, will confirm the subject's eligibility to participate in this study.
- Blood pressure and pulse will be collected 3 times after resting for 5 minutes (with approximately 2 minutes in between each collection) using a manual cuff during the visit. The average of each set of 3 measurements will be used to determine continued participation in the study.
- The "Lifetime Recent" version of the Pediatric/Cognitively Impaired Version C-SSRS should be completed.
- Record historical/concomitant medications as follows:
  - All lifetime psychoactive medications and lifetime non-pharmacological interventions (behavioral therapy) for ADHD
  - Other medications used during the 30 days prior to the screening visit (Visit -1)

### Rating Scales and Assessments

Clinician-completed rating scales and assessments conducted by the site must be completed by the same rater with input from the same parent(s)/LAR whenever possible. The rating scales and assessments are described below.

### Screening Assessments

Kiddie – Schedule for Affective Disorders and Schizophrenia for School age Children – Present and Lifetime Version-Diagnostic Interview (K-SADS-PL)

The sponsor-approved clinician at the site who is trained and experienced in the evaluation of 4- to 5-year-old children with ADHD, will determine a diagnosis of ADHD based on a psychiatric interview and mental status examination utilizing the K-SADS-PL using the DSM IV-TR criteria for ADHD.

The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to Diagnostic and Statistical Manual of Mental Disorders (DSM) IV TR criteria. Probes and objective criteria are provided to rate individual symptoms. The primary diagnoses assessed with the K-SADS-PL include, but are not limited to: major depression, dysthymia, mania, bipolar disorders, schizoaffective disorders, panic disorder, agoraphobia, separation anxiety disorder, avoidant disorder of childhood and adolescence, simple phobia, social phobia, overanxious disorder, generalized anxiety, obsessive compulsive disorder, ADHD, conduct disorder, and oppositional defiant disorder.

The K-SADS-PL is administered by interviewing the parent(s)/LAR(s), the subject, and finally achieving summary ratings, which include all sources of information (parent[s]/LAR, child, school, chart, and other).

The K-SADS-PL will be administered by an individual experienced with the scale and qualified to establish a diagnosis. The site should maintain documentation of the K-SADS-PL training in the site's files. All individuals performing this assessment must be pre-approved by the sponsor or delegated vendor. Based on the above criteria, suitable K-SADS-PL administrators may include physicians, nurse practitioners, or licensed psychologists.

#### Peabody Picture Vocabulary Test-Third Edition

The Peabody Picture Vocabulary Test, Third Edition, measures an individual's receptive (hearing) vocabulary for Standard American English and provides a quick estimate of verbal ability or scholastic aptitude (Dunn and Dunn 1997). For purposes of this study, the Peabody Picture Vocabulary Test, Third Edition, will be used as a proxy for general cognitive ability.

The Peabody Picture Vocabulary Test, Third Edition, will be administered by site personnel with training and experience in general psychological testing. All individuals performing this assessment must be pre-approved by the sponsor or delegated vendor.

#### Efficacy

##### Attention-deficit/Hyperactivity Disorder Rating Scale-IV Preschool Version

The ADHD-RS-IV Preschool Version (McGoey et al. 2007) is completed by the clinician and will be administered at the baseline visit (Visit 0) and each subsequent visit up to and including Visit 6/ET to capture the ADHD symptoms within each study period. The ADHD-RS-IV Preschool Version was adapted from the ADHD Rating Scale-IV (DuPaul et al. 1998) and provides examples appropriate for the developmental level of preschool children. The ADHD-RS-IV Preschool Version is an 18-item questionnaire that requires the respondent to rate the frequency of occurrence of ADHD symptoms as defined by DSM IV TR criteria. Each item is scored on a 4-point scale ranging from 0 (never or rarely) to 3 (very often) with total scores ranging from 0-54. The 18 items may be grouped into 2 subscales: hyperactivity/impulsivity (even numbered items 2-18) and inattentiveness (odd numbered items 1-17).

The ADHD-RS IV Preschool Version will be completed by a clinician trained and experienced in the evaluation of preschool children with ADHD. If it is not completed by the principal investigator or subinvestigator who is medically/clinically responsible for the subject, it must be reviewed and signed by them. All individuals performing this assessment must be pre-approved by the sponsor or delegated vendor.

##### Clinical Global Impressions (CGI)

The Clinical Global Impressions Scale (Guy 1976) permits a global evaluation of the subject's severity and improvement over time. The Clinical Global Impressions Scale has been used extensively in clinical studies of ADHD (Michelson et al. 2001; Weiss et al. 2005; Wilens et al. 2001).

The investigator will perform the CGI-S to rate the severity of a subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects) at the baseline visit (Visit 0). Additionally, at the baseline visit (Visit 0), the investigator should establish 3 target areas of improvement with the subject and the subject's parent(s)/LAR. To generate the targets, an open-ended question such as "If this program of treatment works for your child, what things do you hope he/she will be doing better?" should be asked. Ratings will be completed with respect to ADHD symptoms.

At each visit from Visit 1 up to and including Visit 6ET, the investigator will assess the subject's overall improvement relative to the 3 target areas of improvement recorded at the baseline visit (Visit 0), on the CGI-I, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The CGI-S and CGI-I should be completed by a clinician trained and experienced in the evaluation of preschool children with ADHD. If it is not completed by the principal investigator or sub-investigator who is medically/clinically responsible for the subject, it must be reviewed and signed by them. All individuals performing this assessment must be pre-approved by the sponsor or designee.

**Safety**

Children's Sleep Habits Questionnaire (CSHQ) and Sleep Diary

The CSHQ is a tool designed to screen for the most common sleep problems in children, and consists of 33 items for scoring and several extra items intended to provide administrators with other potentially useful information about respondents. The instrument evaluates the child's sleep based on behavior within 8 different subscales: bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, and daytime sleepiness. The CSHQ will be conducted at each visit to the site starting with the baseline visit (Visit 0) and will be completed by the subject's parent(s)/LAR.

The subject's parent(s)/LAR will complete a sleep diary to log daytime napping and nighttime sleep.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner 2007) is a semistructured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The C-SSRS contains 2 required items pertaining to suicidal ideation, 4 required items pertaining to suicidal behavior, and 1 required item pertaining to non-suicidal but self-injurious behavior. In situations where there is a positive response to the screening questions, there are 8 additional suicidal ideation items and 4 additional suicidal behavior items which are completed. Thus, there is a maximum of 19 items to be completed.

The C-SSRS must be performed by an individual who is medically responsible for the subject. All individuals performing this assessment must be pre-approved by the sponsor or delegated vendor.

The Pediatric/Cognitively Impaired Version of the scale will be used in the study. Two time point versions of the C-SSRS are used in this study:

- The "Lifetime Recent" version will be administered at the screening visit (Visit -1).
- The "Since Last Visit" version will be completed at all study visits after the screening visit (Visit -1).

**Inclusion and exclusion criteria:**

**Inclusion Criteria:**

The subject will not be considered eligible for the study without meeting all of the criteria below (including test results).

1. Subject is a male or female aged 4-5 years inclusive at the time of consent.
2. Subject's parent(s) or legally authorized representative (LAR) must provide signature of informed consent, and there must be documentation of assent (if applicable) by the subject in accordance the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996), any updates or revisions, and applicable regulations, before completing any study related procedures.
3. Subject and parent(s)/LAR are willing and able to comply with all of the testing and requirements defined in the protocol, including oversight of morning dosing. Specifically, the parent(s)/LAR must be available at approximately 7:00AM ( $\pm 2$  hours) to dispense the dose of investigational product for the duration of the study.
4. Subject must meet Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV-TR) criteria for a primary diagnosis of ADHD (any subtype) based on a detailed psychiatric evaluation.
5. Subject has an ADHD-RS-IV Preschool Version Total Score at the baseline visit (Visit 0) of  $\geq 28$  for boys, and  $\geq 24$  for girls.
6. Subject has a CGI-S score  $\geq 4$  at the baseline visit (Visit 0).

7. Subject has a Peabody Picture Vocabulary Test standard score of  $\geq 70$  at the screening visit (Visit -1).
8. Subject has undergone an adequate course of non-pharmacological treatment OR the subject has a severe enough condition to consider enrollment without undergoing prior non-pharmacological treatment, based on investigator judgment.
9. Subject has, in the opinion of the investigator, participated in a structured group activity (eg, preschool, sports, Sunday school) so as to assess symptoms and impairment in a setting outside the home.
10. Subject has lived with the same parent(s) or guardian for  $\geq 6$  months.

**Exclusion Criteria:**

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Subject is required to or anticipates the need to take any prohibited medications or medications that have central nervous system (CNS) effects or have an effect on performance, such as sedating antihistamines and decongestant sympathomimetics, or other monoamine oxidase inhibitors. Stable use of bronchodilator inhalers is not exclusionary.
2. Subject has taken another investigational product or has taken part in a clinical study within 30 days prior to the screening visit (Visit -1).
3. Subject is well-controlled on his/her current ADHD medication with acceptable tolerability.
4. Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments conducted in the study or that might increase risk to the subject. Similarly, the subject will be excluded if he or she has any additional condition(s) that, in the investigator's opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. The additional conditions would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable asthma is not exclusionary.
5. Subject has glaucoma.
6. Subject has failed to fully respond, based on investigator judgment, to an adequate course of amphetamine therapy.
7. Subject has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
8. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
9. Subject has a blood pressure measurement  $\geq 95$ th percentile for age, sex, and height at the screening visit (Visit -1) or the baseline visit (Visit 0), or a history of moderate or severe hypertension
10. Subject has a known history of:
  - symptomatic cardiovascular disease
  - unexplained syncope
  - exertional chest pain
  - advanced arteriosclerosis
  - structural cardiac abnormality
  - cardiomyopathy
  - serious heart rhythm abnormalities
  - coronary artery disease
  - other serious cardiac problems placing them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

11. Subject has any clinically significant laboratory abnormalities at the screening visit (Visit -1) or clinically significant ECG at the screening visit (Visit -1) or baseline visit (Visit 0) based on investigator judgment.
12. Subject has a history of hyperthyroidism or current abnormal thyroid function, defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4) at the screening visit (Visit -1). Treatment with a stable dose of thyroid medication for at least 3 months is permitted.
13. Subject has a current, controlled (requiring medication or therapy) or uncontrolled, co-morbid psychiatric disorder including but not limited to any of the below co-morbid Axis I disorders and Axis II disorders:
  - i. post-traumatic stress disorder or adjustment disorder
  - ii. bipolar illness, psychosis, or a family history of these disorders
  - iii. pervasive developmental disorder
  - iv. obsessive-compulsive disorder (OCD)
  - v. psychosis/schizophrenia
  - vi. a serious tic disorder, or a family history of Tourette's disorder
  - vii. Subject is currently considered a suicide risk in the opinion of the investigator, has previously made a suicide attempt, or has a prior history of, or is currently demonstrating active suicidal ideation.
  - viii. a history of physical, sexual, or emotional abuse
  - ix. any other disorder or agitated state that in the opinion of the investigator, contraindicates SPD489 or lisdexamfetamine dimesylate treatment or confound efficacy or safety assessments.
14. Subject has initiated behavioral therapy within 1 month of the baseline visit (Visit 0). Subject may not initiate behavioral therapy during the study.
15. Subject has a height  $\leq$ 5th percentile for age and sex at the screening visit (Visit -1).
16. Subject has a weight  $\leq$ 5th percentile for age and sex at the screening visit (Visit -1).
17. Subject lives with anyone who currently abuses stimulants or cocaine.
18. Subject has a history of seizures (other than infantile febrile seizures).
19. Subject is taking any medication that is excluded per the protocol.

**Duration of subject involvement in the study:**

- Planned duration of screening period: 28 days
- Planned duration of treatment period: 42 days
- Planned duration of safety follow-up period: 7 days

**Endpoints and statistical analysis:**

**Subject Populations**

The **Screened Set** will consist of all subjects who have signed an informed consent.

The **Randomized Set** will consist of all subjects in the Screened Set for whom a randomization number has been assigned.

The **Safety Analysis Set** will consist of all subjects in the Randomized Set who have taken at least 1 dose of investigational product.

The **Full Analysis Set (FAS)** will consist of all subjects in the Safety Analysis Set who have at least 1 post-baseline ADHD-RS-IV-Preschool Version Total Score assessment, where baseline is defined as the last valid assessment prior to taking the first dose of investigational product.

The **Dose Response Analysis Set (DRAS)** will consist of all subjects in the Safety Analysis Set who have at least 1 valid primary efficacy measurement (ADHD-RS total score) on the randomized target dose strength of the investigational product.

The above analysis sets are similarly defined for both the interim and the complete study analyses.

#### **Primary Efficacy Endpoint**

The primary efficacy endpoint is defined as the change from baseline in clinician-administered ADHD-RS-IV Preschool Version Total Score at Visit 6 (Week 6).

#### **Key Secondary Efficacy Endpoint**

The key secondary efficacy endpoint is the improvement status based on CGI-I measurement at Visit 6 (Week 6).

#### **Secondary Efficacy Endpoint**

A secondary efficacy endpoint is the dose response relationship of SHP489 for randomized fixed-dose strength (placebo, SHP489 5, 10, 20, and 30 mg), as measured by the change from baseline for ADHD-RS Preschool Version Total Score at study stop (at interim analysis or end of study).

#### **Safety Endpoints**

Safety assessments include the occurrence of TEAEs, specific evaluation of blood pressure, pulse, height, weight, and body mass index, clinical laboratory evaluations and ECG results, sleep assessments (including sleep diary data and CSHQ), and C-SSRS.

#### **Statistical Methodology for Primary Efficacy Endpoint(s)**

For the primary and key secondary efficacy analyses the SPD489 10, 20, and 30 mg dose strengths will be pooled together to compare with placebo group in change from baseline. For these analyses the SPD489 5 mg data will not be used.

Primary efficacy endpoint will be analyzed using the linear mixed-effects model for repeated measures (MMRM) with treatment group, visit, and the interaction of treatment group with visit as factors, baseline ADHD-RS-IV Preschool Version Total Score as a covariate, and the interaction of the baseline ADHD-RS-IV Preschool Version Total Score with visit adjusted in the model. The primary contrast of interest will be pooled 10, 20, and 30 mg dose treatment assessment at Visit 6 (Week 6) for SPD489 compared with placebo. The 2-sided overall significance level for the primary endpoint analysis is 0.05. The nominal significance levels used at the interim and final analysis are described in the Interim Analysis section below.

#### *Interim Analysis*

The study implements a group sequential design with one interim analysis. The interim analysis is proposed at approximately 60% of planned subjects who either complete or discontinue the study.

The interim analysis will be conducted on the interim analysis dataset, which is defined as all data from 60% of initially planned subjects who have either completed or discontinued the study, together with data for subjects in the study up to the interim analysis data cut time point. The efficacy, safety, and sensitivity on missing data mechanisms analyses at the interim analysis will primarily be conducted using this dataset.

The Lan-DeMets alpha spending function with O'Brien-Fleming boundary will be used for alpha spending between the interim and end of study analysis for the primary endpoint. The Lan-DeMets alpha spending function with Pocock boundary will be applied to analyze the key secondary efficacy endpoint.

If the hypothesis for the primary efficacy endpoint is rejected at the interim analysis, then the study will be stopped for efficacy and all ongoing subjects from the study (SPD489-347) will be immediately rolled over to the open-label extension study (Study SPD489-348). In this case, using the same data cut point that contains the same information fractions as the primary efficacy interim analysis, the key secondary efficacy endpoint will be tested. In addition, the incremental data collected during the interim analysis process, i.e., the overrun, together with the interim analysis dataset will be used for primary and key secondary sensitivity analysis and all safety

analysis. Otherwise, if the primary efficacy criterion is not met at the interim analysis, then the hypothesis for the key secondary endpoint will not be tested at this time, and the study will continue to its completion, then the primary efficacy endpoint will be tested. If the primary efficacy test is rejected, then the key secondary efficacy endpoint will be tested. This testing procedure strongly protects the overall alpha level. In addition, all other efficacy and safety analyses will be conducted at this time.

At the interim or final efficacy analysis, only the primary efficacy result will be used to determine if the study meets the efficacy criterion. The nominal significance level for the interim or final primary and key secondary efficacy endpoints for a 2-sided at a 0.05 significant level are specified below, calculated using East<sup>®</sup> 6.4. The calculations are based on 60% of planned sample size, and will be updated based on the actual information fraction at the interim analysis.

	Efficacy Boundary p-value Scale	
	Interim Analysis	Final Analysis
Primary Endpoint	0.0074	0.0477
Key Secondary Endpoint	0.0354	0.0257

Separately, if the primary efficacy criterion is met at the interim analysis, the interim analysis dataset together with overrun data will be used to evaluate the dose-response relationship with the DRAS. If the primary efficacy criterion is not met at the interim analysis and study continues to its completion, dose-response evaluation will be conducted using the end of study data.

If the primary efficacy criterion is not met at the interim analysis, and the blinded sample size re-estimation causes a sample size increase, the nominal significance levels at the end of the study will be recalculated, such that the overall alpha level is not greater than 0.05 for the primary and key secondary analyses together. The calculations will be based on the new increased sample size, the actual information ratio, and the alpha already spent.

It is estimated that the interim analysis will take up to 8 weeks from data cutoff to its completion. If the recruitment rate is high and the remaining 40% planned subjects are projected to be all or nearly all enrolled within those 8 weeks, the interim analysis will be waived with reasons documented. In this case, the end of study analysis will be conducted at the 2-sided significance level of 0.05 with primary and key secondary endpoints tested sequentially. Furthermore, the dose-response relationship will be evaluated.

#### Statistical Methodology for Secondary Efficacy Endpoints

- The key secondary efficacy endpoint, CGI-I score, will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The baseline CGI-S score will be used as the covariate. The contrast of interest will be at Visit 6 (Week 6) for SPD489 compared with placebo.
- The dose-response relationship of SPD489 as measured by the change from baseline for ADHD-RS Preschool Version Total Score for the randomized fixed-dose arms (placebo, SHP489 5, 10, 20, and 30 mg) will be evaluated using the MCP-Mod methodology with DRAS.

#### Safety Analyses

The Safety Analysis Set will be used to report the safety data.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit using appropriate descriptive statistics. Potentially clinically important findings will also be summarized or listed by treatment group.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events are defined as adverse events (AEs) that start or deteriorate on or after the date of the first dose of investigational product and no later than 3 days following the last dose of investigational product in the double-blind phase.

Treatment-emergent AEs will be summarized. The number and percent of subjects with TEAEs will be calculated for each system organ class, by preferred term, and by treatment. The severity of the TEAEs, the relationship to the investigational product, TEAEs causing study discontinuation, serious AEs and death will also be presented.

The CSHQ will also be summarized using appropriate descriptive statistics.

Sleep diary data will be descriptively summarized.

A summary and listing of the C-SSRS data will be provided for subjects with a positive response only.

#### **Data Monitoring Committee**

An external independent Data Monitoring Committee (DMC) was set up to review the data pertaining to safety, tolerability, and benefit/harm of the study therapy for the duration of this Pediatric Written Request program, which includes studies SPD489-211, SPD489-347, and SPD489-348. The same DMC will evaluate the efficacy analysis results and supportive safety summaries to determine if the interim efficacy criteria are met for this study. Confidentiality of the unblinded DMC analyses is a critical concern, and to address this, an un-blinded independent reporting team will be identified within a CRO. The independent reporting team will have no involvement in the conduct of the study.

#### **Sample Size Re-estimation**

In order to have sufficient study power to detect a clinically meaningful treatment effect for the primary efficacy endpoint, a blinded sample size re-estimation is planned as described in the section "Number of Subjects".

**STUDY SCHEDULE(S)**

**Table 1 Schedule of Assessments**

Period	Screening and Washout			Dose-titration			Dose-maintenance			Safety Follow-up
	-1 (Screening)	Washout Telephone Call	0 (Baseline)	1	2	3	4	5	6/ ET	Telephone Call
Assessment Week	-4 to -1	-1	0	1	2	3	4	5	6	7
Assessment Day	-28 to -1		0	7	14	21	28	35	42	49
Informed consent/assent	✓									
Psychiatric evaluation (utilizing the K-SADS-PL)	✓									
Peabody Picture Vocabulary Test	✓									
Inclusion/exclusion criteria	✓	✓ <sup>b</sup>	✓ <sup>b</sup>							
Demographics	✓									
Randomization			✓							
Medical and medication history <sup>c</sup>	✓									
Physical examination	✓		✓ <sup>d</sup>						✓	
Vital signs <sup>e</sup>	✓		✓	✓	✓	✓	✓	✓	✓	
Height <sup>f</sup>	✓								✓	
Body weight <sup>f</sup>	✓		✓	✓	✓	✓	✓	✓	✓	
Calculate BMI <sup>g</sup>	✓									
Clinical laboratory tests <sup>h, i</sup>	✓		✓ <sup>d</sup>						✓	
12-lead ECG <sup>j</sup>	✓		✓ <sup>d</sup>	✓	✓	✓	✓	✓	✓	
ADHD-RS-IV Preschool Version <sup>k</sup>			✓	✓	✓	✓	✓	✓	✓	
CGI-S <sup>l</sup>			✓							

**Table 1 Schedule of Assessments**

Period	Screening and Washout			Dose-titration			Dose-maintenance			Safety Follow-up
	-1 (Screening)	Washout Telephone Call	0 (Baseline)	1	2	3	4	5	6/ ET	Telephone Call
Assessment Week	-4 to -1	-1	0	1	2	3	4	5	6	7
Assessment Day	-28 to -1		0	7	14	21	28	35	42	49
CGI-I <sup>k</sup>				✓	✓	✓	✓	✓	✓	
CSHQ <sup>k</sup>			✓	✓	✓	✓	✓	✓	✓	
Sleep diary <sup>l</sup>			✓	✓	✓	✓	✓	✓	✓	
C-SSRS <sup>k</sup>	✓		✓	✓	✓	✓	✓	✓	✓	
Suitability of subject to remain in study <sup>m</sup>			✓	✓	✓	✓	✓	✓		
Access IWRS	✓		✓	✓	✓	✓	✓	✓	✓	
Investigational product distributed			✓	✓	✓	✓	✓	✓		
Investigational product returned				✓	✓	✓	✓	✓	✓	
Investigational product compliance				✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

ADHD-RS-IV=ADHD Rating Scale-IV; BMI=body mass index; CGI-I=Clinical Global Impressions-Global Improvement; CGI-S=Clinical Global Impressions-Severity of Illness; CSHQ=Children's Sleep Habits Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=Electrocardiogram; ET=early termination; IWRS= Interactive Web Response System; K-SADS-PL=Kiddie-Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version-Diagnostic Interview

<sup>a</sup> Visit windows are ±3 days [in reference to the baseline visit (Visit 0) date] during the Fixed-dose titration and Dose-maintenance Periods. Safety Follow-up Telephone Call window is +3 days.

<sup>b</sup> Inclusion/exclusion criteria must be reviewed at the Washout Telephone Call and at the baseline visit (Visit 0).

<sup>c</sup> Medication history will include a lifetime history of pharmacologic and non-pharmacologic therapies for ADHD.

<sup>d</sup> An abbreviated physical examination, 12-lead ECG, and all clinical laboratory tests must be repeated and results reviewed by the investigator prior to the baseline visit (Visit 0) if more than 30 days have elapsed since the safety measurements at the screening visit (Visit -1) were collected. Results must be obtained and reviewed prior to determining eligibility.

**Table 1 Schedule of Assessments**

Period	Screening and Washout			Dose-titration			Dose-maintenance			Safety Follow-up
	-1 (Screening)	Washout Telephone Call	0 (Baseline)	1	2	3	4	5	6/ ET	Telephone Call
Assessment Week	-4 to -1	-1	0	1	2	3	4	5	6	7
Assessment Day	-28 to -1		0	7	14	21	28	35	42	49

<sup>e</sup> Includes oral or tympanic temperature, sitting blood pressure, pulse, and respiratory rate. Measurements of blood pressure and pulse will be performed at each visit to the site. Measurements of temperature and respiratory rate will be performed at the screening visit (Visit -1) and Visit 6/ET only. Blood pressure, pulse, and respiratory rate will be determined after subjects have remained seated for a minimum of 5 minutes. Measurement of blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using a manual cuff. The average of each set of 3 measurements will be used to determine continued participation in the study. Blood pressure measurements should be taken prior to the collection of blood draws.

<sup>f</sup> Height and weight to be measured without shoes.

<sup>g</sup> BMI will be recorded at Screening for eligibility. BMI will be derived from height and weight during the course of the study for analysis.

<sup>h</sup> Clinical laboratory tests will include hematology, chemistry, endocrinology, and urinalysis.

<sup>i</sup> Patients will have the option for blood draws to be collected by a home health care professional at their home. Home draws have a ±1 day window from the study visit date, with the exception of the 6/ET home draw which has a -1 day window.

<sup>j</sup> Three ECGs, taken approximately 5 minutes apart, are to be collected so that appropriate baseline intervals are established. Results must be reviewed prior to determining eligibility.

<sup>k</sup> Scales to be completed by same rater with input from the same parent/LAR whenever possible.

<sup>l</sup> Sleep diary to be completed by parent(s)/LAR. Sleep diaries will be dispensed at Visits 0-5 and collected at Visits 1-6.

<sup>m</sup> C-SSRS “Lifetime Recent” version completed at the screening visit (Visit -1). C-SSRS “Since Last Visit” version completed for all subsequent visits. Include assessment of decreased appetite.

## 1 BACKGROUND INFORMATION

Lisdexamfetamine dimesylate capsules (SPD489, previously referred to as NRP104) were developed for the once-daily treatment of attention-deficit/hyperactivity disorder (ADHD).

SPD489 capsules contain 5, 10, 20, or 30 mg of lisdexamfetamine dimesylate, a new chemical entity designed for once-daily oral administration. Lisdexamfetamine itself is a pharmacologically inactive prodrug. After ingestion it is converted to *l*-lysine (a naturally occurring essential amino acid) and dextroamphetamine (*d*-amphetamine, responsible for pharmacological activity) primarily in the blood.

Amphetamine is a chiral compound that exists as 2 stereoisomers: *d*- and levo (*l*)-amphetamine. Lisdexamfetamine is the *l*-lysine conjugate of the dextro stereoisomer. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted primarily in the blood to *l*-lysine (a naturally occurring amino acid) and *d*-amphetamine, which is responsible for the drug's pharmacological activity.

Lisdexamfetamine is classified as a psychomotor stimulant.

Amphetamine appears to exert its pharmacological effects in the central nervous system (CNS) by increasing the availability of naturally occurring amines that have important functions in nerve terminals. Amphetamine increases synaptic levels of dopamine, norepinephrine, and serotonin through multiple mechanisms (Hardman et al. 2001). It promotes the release of dopamine, norepinephrine, and serotonin into the extraneuronal space, and also inhibits the reuptake of dopamine and norepinephrine into the pre-synaptic nerve terminal resulting in prolonged residency of these neurotransmitters in the synaptic cleft. In addition to producing a CNS response, amphetamine treatment is also associated with cardiovascular effects such as an increase in systolic blood pressure and diastolic blood pressure, and pulse. Amphetamine may also suppress the appetite.

In addition to the approved indication of ADHD, other indications have been explored.

Additional information can be found in the current investigator's brochure (IB) for SPD489.

### 1.1 Indication and Current Treatment Options

Attention-deficit/hyperactivity disorder is a heterogeneous neurobehavioral disorder characterised by a pattern of developmentally inappropriate inattentiveness, impulsivity, and hyperactivity resulting in clinically significant impairment in social, academic, or occupational functioning. Although ADHD was originally thought to be a disorder primarily affecting elementary school age children; it is now recognized that ADHD may persist across a lifetime, and that ADHD symptoms may manifest several years prior to entry into elementary school.

While there are hundreds of studies investigating the treatment of ADHD in school-age children, there are very few studies exploring the treatment of ADHD in preschoolers. Although diagnosing ADHD in a preschool child can be challenging, reliable diagnostic tools and age-appropriate assessments are available, and it is therefore possible to conduct scientifically

rigorous ADHD studies in this population. It would be beneficial to provide additional evidence-based support for ADHD treatment decisions in the preschool population.

Estimates of the prevalence of ADHD in the preschool population vary depending on the referral source and the method used to diagnose ADHD; however it appears that approximately 4-5% of preschool children are considered to have ADHD. Using the Preschool-age Psychiatric Assessment, an assessment validated for use in the preschool population, the prevalence of ADHD in a sample of 1,073 children aged 2-5 years was reported to be 3.9-5.1% (Egger et al. 2006a; Egger and Angold 2004; Greenhill et al. 2008). In 2007, the National Survey of Children's Health obtained information from parents of 73,123 children aged 4-17 years (Centers for Disease Control and Prevention 2010). Parents reported a current diagnosis of ADHD in 5.5% of 4- to 10-year-olds (Centers for Disease Control and Prevention 2010). Some reports utilizing a clinic-based sampling frame (versus a community based - sampling frame) report the prevalence in males aged 4-11 is roughly 3 times greater than in females (Szatmari et al. 1989). There is acknowledgment, however, that males present with more disruptive symptoms and are referred for treatment earlier and more often than girls (Hinshaw 2002), so clinic samples are not likely to represent an accurate reflection of the gender distribution of ADHD.

Genetic studies indicate that ADHD has high heritability rates (Faraone and Biederman 1998; Tannock 1998) with an autosomal rather than sex-linked inheritance pattern (Wallis et al. 2008; Thapar 2002) supporting the gender-based prevalence ratios of 1:1 in the community which is consistent with the reported 1:1 male:female prevalence of ADHD in adults.

Attention-deficit/hyperactivity disorder is characterized by symptoms of inattention, hyperactivity, and impulsivity that are "maladaptive and inconsistent with developmental level" (Diagnostic and Statistical Manual of Mental Disorders [DSM-IV]). Preschool children, ages 3-5 years, often exhibit symptoms of hyperactivity and impulsivity, so it may be challenging to delineate what is "inconsistent with developmental level" for this population (Smith and Corkum 2007). Nevertheless, it is possible to diagnose ADHD in the preschool population in a reliable fashion (Egger et al. 2006a; Egger et al. 2006b; McGoey et al. 2007).

The presence of ADHD symptoms that are frequent, severe, and developmentally inappropriate can be used to define ADHD in this population (Connor 2002; Smith and Corkum 2007). In addition, impairment in 2 or more settings establishes that the constellation of ADHD symptoms is maladaptive and not confined to a specific environment. The severity of ADHD symptoms in a preschool child can be reliably measured using scales such as the Preschool-age Psychiatric Assessment and the ADHD-Rating Scale-IV Preschool Version (ADHD-RS-IV Preschool Version) that have been validated for this population and include age-appropriate questions and prompts (Egger et al. 2006a; McGoey et al. 2007).

It is appropriate to consider whether an ADHD diagnosis in a preschool child will endure or resolve as the child matures. ADHD has been described in terms of a developmental trajectory that can be modified by biologic or environmental factors (Sonuga-Barke and Halperin 2010; Sonuga-Barke et al. 2005). Potential risk factors such as severity of ADHD symptoms, the presence of oppositional defiant symptoms, and neuropsychological impairment may affect the course of ADHD (Sonuga-Barke and Halperin 2010).

Although some children may not retain the ADHD diagnosis as they grow older, for many children the diagnosis endures beyond their preschool years (Lahey et al. 2004; Tandon et al. 2011). In a sample of 96 children aged 4-6 years with ADHD, 79% of the children continued to have an ADHD diagnosis 3 years later as compared to 3% of the non-ADHD control children (Lahey et al. 2004). This finding was replicated in a sample of 48 children aged 4-6 years with ADHD who were followed for 2 years (Tandon et al. 2011). These results suggest that when an ADHD diagnosis is first made in a preschool child, it is likely to be stable over time.

The constellation of impairments associated with an ADHD diagnosis in preschool children suggests a characteristic profile similar to that for individuals diagnosed after the preschool period. Preschool children with ADHD demonstrate impairments in social functioning and pre-academic skills (DuPaul et al. 2001; Ghuman et al. 2008). They are also more likely to be aggressive towards others and to sustain an injury (Greenhill et al. 2008; Rappley et al. 1999). In a longitudinal study which followed children aged 4-21 years, the attention span at age 4 years predicted math and reading skills at age 21 years and completion of college at age 25 years (McClelland et al. 2013).

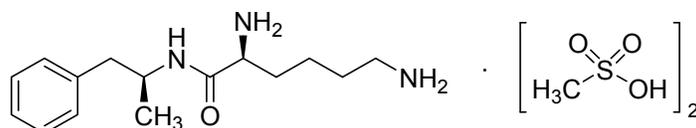
Currently, the lack of a robust body of evidence derived from controlled clinical studies in preschool children makes it difficult to create reliable treatment recommendations. The American Academy of Pediatrics (AAP) ADHD Clinical Practice guideline suggests that preschool children with ADHD initiate treatment with behavioral therapy prior to using pharmacotherapy (Subcommittee on ADHD et al. 2011); however the Preschool ADHD Treatment Study results indicates that only 13% of preschool children have a satisfactory response to behavioral therapy (Greenhill et al. 2006). If the preschool child with ADHD does not respond to behavioral therapy, the guideline then suggests the use of methylphenidate. Of note, methylphenidate does not have an indication for a population less than 6 years old (Subcommittee on ADHD et al. 2011). Immediate-release ADDERALL (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, and amphetamine sulfate) and dextroamphetamine are approved for children with ADHD as young as 3 years old. As a result, if a preschool child does not respond to methylphenidate, a trial of an amphetamine product is recommended by the AAP. However, the lack of data for amphetamines in preschool children with ADHD is acknowledged. Therefore the implementation of additional studies in preschool children with ADHD would provide additional evidence in order to inform treatment decisions.

## 1.2 Product Background and Clinical Information

The active pharmaceutical ingredient of SPD489 is (2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate.

Figure 1 shows the chemical structure of the active pharmaceutical ingredient:

**Figure 1 Chemical Structure of the Active Pharmaceutical Ingredient**



Always refer to the latest version of the SPD489 IB for the most accurate and current information regarding the efficacy and safety of SPD489.

### 1.2.1 Preclinical Information

Lisdexamfetamine is a pharmacologically inactive prodrug. After ingestion, it is converted in the blood to *d*-amphetamine (responsible for pharmacological activity) and *l*-lysine (a naturally occurring essential amino acid). A comprehensive set of studies has been conducted to evaluate the pharmacological and toxicological properties associated with the parent compound lisdexamfetamine. The safety profiles associated with *d*-amphetamine and *l*-lysine are well established.

All safety and toxicology studies, except the single-dose acute toxicity study in rats, were conducted in compliance with Good Laboratory Practice.

Complete preclinical information is presented in the current SPD489 IB.

### 1.2.2 Clinical Information

The pharmacological profile of lisdexamfetamine and the pharmacologically active metabolite *d*-amphetamine have been well-characterized in studies enrolling children, healthy adults, and adults with a history of stimulant abuse. These studies have demonstrated that oral administration of SPD489 resulted in a predictable *d*-amphetamine pharmacokinetic profile with low intrasubject and intersubject variability. The *d*-amphetamine  $AUC_{0-\infty}$  and  $C_{max}$  generally behaved in a linear, dose-proportional manner. The weight-normalized *d*-amphetamine  $AUC_{0-\infty}$  is similar for children and adults, with  $t_{max}$  and  $t_{1/2}$  consistent across age groups.

In the ADHD Clinical Development Program, the efficacy of SPD489 for the treatment of ADHD has been demonstrated for children, adolescents, and adults with ADHD. Substantial evidence of efficacy was provided in well-controlled studies, where SPD489 was shown to be effective compared to placebo. SPD489 was associated with a statistically significant, clinically meaningful improvement in ADHD symptoms, functional outcomes, and health-related quality of life compared to placebo, in studies that used a variety of study designs, a variety of validated assessments, and a variety of raters.

The well-characterized SPD489 safety profile was consistent with that of other stimulants used in the treatment of ADHD. When the safety results from the 15 completed Phase 2-4 clinical studies in the ADHD Clinical Development Program were examined, the majority of TEAEs were mild or moderate in severity, and no differences due to age or sex were noted. The most frequently reported adverse events (AEs) were those typically associated with stimulant therapy (including decreased appetite, insomnia, headache, dry mouth, irritability, upper abdominal pain, and weight decrease), or potentially attributable to intercurrent illnesses (eg, upper respiratory tract infection and nasopharyngitis). These TEAEs were generally non-serious and were considered by the investigator to be resolved during study participation.

Stimulant medications like SPD489 cause a modest increase in average blood pressure (about 2-4 mmHg) and average pulse (about 3-6 bpm). Individuals may have larger increases.

Always refer to the latest version of the SPD489 IB for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SPD489.

## 2 STUDY OBJECTIVES AND PURPOSE

### 2.1 Rationale for the Study

Based on IMS Health data and discussion at the Food and Drug Administration (FDA) Pediatric Advisory Committee in September 2012 ([Mistry and Chai 2012](#)), it has been noted that there is off-label use of SPD489 in children under 5 years old (4%, or approximately 100,000 patients between February 2007 and March 2012). The lack of controlled data regarding the safety and efficacy of SPD489 in the preschool ADHD population, in concert with the prevalence of off-label prescribing of SPD489 supports the need for SPD489 studies in the preschool ADHD population. Importantly, it is not known if the therapeutic effects of stimulant medications in school age children with ADHD can be extrapolated to preschool children with ADHD. There are some indications that the effect size may be reduced ([Greenhill et al. 2006](#)). There may also be differences in the safety and pharmacokinetic profiles ([Wigal et al. 2007](#); [Wigal et al. 2006](#)).

However, recent data from Shire SPD489-211 study preschool aged children with ADHD suggests the safety and tolerability profile of SHP489 is similar to that observed in trials with children 6 to 12 years old, adolescents and adults. The efficacy results of the SPD489-211 study, were also comparable to older subjects and revealed a mean decrease from baseline of -26.1 (95% CI: -32.2, -20.0) in the ADHD-RS-IV Preschool Version total score, suggesting a robust similar improvement in ADHD symptoms.

In summary given the abundance of information regarding the safety and efficacy of amphetamines; the very well-established PK profile of SPD489; the similar efficacy and safety findings between populations with ADHD covering the age span from 6 to 55 years; and the PK, safety, and efficacy data from Study SPD489-211 in preschoolers (aged 4-5 years) with ADHD, it is expected that findings from previous trials in older age groups can be extrapolated to preschool patients with ADHD.

### 2.2 Study Objectives

#### 2.2.1 Primary Objectives

To evaluate the efficacy of SPD489 compared to placebo in preschool children (4-5 years of age inclusive at the time of consent) with ADHD. The primary measure of efficacy will be the clinician-administered ADHD Rating Scale Preschool Version (ADHD-RS-IV Preschool Version) Total Score.

#### 2.2.2 Secondary Objectives

- **Key secondary:** To evaluate the efficacy of SPD489 compared to placebo, using the global clinical measure of improvement, the Clinical Global Impression-Global Improvement (CGI-I) Scale.

- **Secondary:**
  - To evaluate the dose response relationship in preschool children with ADHD, using the ADHD-RS Preschool Version Total Score.
  - To evaluate the safety and tolerability of SPD489 based on the occurrence of treatment-emergent adverse events (TEAEs), specific evaluation of vital signs (systolic and diastolic blood pressure and pulse), height, weight, and body mass index (BMI), clinical laboratory evaluations, and electrocardiogram (ECG) results, sleep assessment, and the Columbia Suicide Rating Scale (C-SSRS).

### 3 STUDY DESIGN

#### 3.1 Study Design and Flow Chart

Approximately 245 subjects will be screened to randomize approximately 195 subjects in a 5:5:5:5:6 ratio to SPD489 5, 10, 20, 30 mg dose strength or placebo to achieve 156 completers for this Phase 3 double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy of SPD489 10, 20, and 30 mg pooled together compared to placebo, administered as a daily morning dose in the treatment of preschool children 4-5 years of age with ADHD.

Approximately 25% of the subjects enrolled will be female, consistent with the literature-defined gender distribution in ADHD clinic samples ([Szatmari et al. 1989](#); [Wallis et al. 2008](#); [Thapar 2002](#)).

A randomized fixed-dose design is used to avoid baseline characteristics selection bias for different treatment groups on the part of the participants and investigators. Blinded treatment is used to reduce potential bias during data collection and evaluation of clinical results. The placebo arm is used to control the subject's expectation that a treatment would have an effect, to optimize sensitivity, to maintain the scientific rigor of the study, and to validate the study internally.

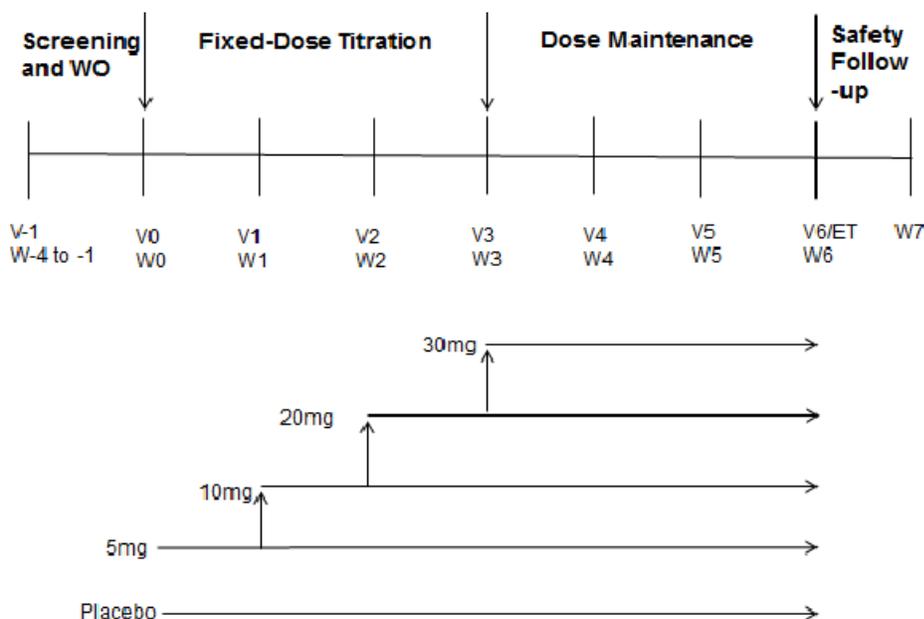
The study will have 4 periods as outlined below and in [Figure 2](#):

- (1) Screening and Washout
- (2) Fixed-dose titration
- (3) Dose-maintenance
- (4) Safety Follow-up.

The duration of the double-blind evaluation period (Fixed-dose titration and Dose-maintenance Periods) will be 6 weeks.

SPD489 will be provided in dose strengths of 5, 10, 20, and 30 mg. Matching placebo will also be provided.

Figure 2 Study Design Flow Chart



ET=early termination; V=visit; W=week, WO=washout.

### 3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 11 weeks. The study will be completed in approximately 24 months.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

### 3.3 Sites and Regions

This study will be conducted in up to 60 sites in North America.

## 4 STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent and/or assent, as per IRB/EC requirements, before any procedures specified in the protocol are performed.

### 4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below (including test results).

1. Subject is a male or female aged 4-5 years inclusive at the time of consent.
2. Subject's parent(s) or legally authorized representative (LAR) must provide signature of informed consent, and there must be documentation of assent (if applicable) by the subject in accordance with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996), any updates or revisions, and applicable regulations, before completing any study related procedures.
3. Subject and parent(s)/LAR are willing and able to comply with all of the testing and requirements defined in the protocol, including oversight of morning dosing. Specifically, the parent(s)/LAR must be available at approximately 7:00AM ( $\pm 2$  hours) to dispense the dose of investigational product for the duration of the study.
4. Subject must meet DSM-IV-TR criteria for a primary diagnosis of ADHD (any sub-type) based on a detailed psychiatric evaluation.
5. Subject has an ADHD-RS-IV Preschool Version Total Score at the baseline visit (Visit 0) of  $\geq 28$  for boys and  $\geq 24$  for girls.
6. Subject has a Clinical Global Impressions – Severity of Illness (CGI-S) score  $\geq 4$  at the baseline visit (Visit 0).
7. Subject has a Peabody Picture Vocabulary Test standard score of  $\geq 70$  at the screening visit (Visit -1).
8. Subject has undergone an adequate course of non-pharmacological treatment OR the subject has a severe enough condition to consider enrollment without undergoing prior non-pharmacological treatment, based on investigator judgment.
9. Subject has, in the opinion of the investigator, participated in a structured group activity (eg, preschool, sports, Sunday school) so as to assess symptoms and impairment in a setting outside the home.
10. Subject has lived with the same parent(s) or guardian for  $\geq 6$  months.

#### **4.2 Exclusion Criteria**

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Subject is required to or anticipates the need to take any prohibited medications or medications that have CNS effects or have an effect on performance, such as sedating antihistamines and decongestant sympathomimetics, or other monoamine oxidase inhibitors. Stable use of bronchodilator inhalers is not exclusionary.
2. Subject has taken another investigational product or has taken part in a clinical study within 30 days prior to the screening visit (Visit -1).
3. Subject is well-controlled on his/her current ADHD medication with acceptable tolerability.
4. Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments conducted in the study or that might increase risk to the subject.

Similarly, the subject will be excluded if he or she has any additional condition(s) that, in the investigator's opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. The additional conditions would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable asthma is not exclusionary.

5. Subject has glaucoma.
6. Subject has failed to fully respond, based on investigator judgment, to an adequate course of amphetamine therapy.
7. Subject has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
8. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
9. Subject has a blood pressure measurement  $\geq 95$ th percentile for age, sex, and height at the screening visit (Visit -1) or the baseline visit (Visit 0) or a history of moderate or severe hypertension.
10. Subject has a known history of
  - symptomatic cardiovascular disease
  - unexplained syncope
  - exertional chest pain
  - advanced arteriosclerosis
  - structural cardiac abnormality
  - cardiomyopathy
  - serious heart rhythm abnormalities
  - coronary artery disease
  - other serious cardiac problems placing them at increased vulnerability to the sympathomimetic effects of a stimulant drug.
11. Subject has any clinically significant clinical laboratory abnormalities at the screening visit (Visit -1) or ECG at screening visit (Visit -1) or baseline visit (Visit 0) based on investigator judgment.
12. Subject has a history of hyperthyroidism, or current abnormal thyroid function, defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4) at the screening visit (Visit -1). Treatment with a stable dose of thyroid medication for at least 3 months is permitted.
13. Subject has a current, controlled (requiring medication or therapy) or uncontrolled, co-morbid psychiatric disorder including but not limited to any of the below co-morbid Axis I disorders and Axis II disorders:
  - i. post-traumatic stress disorder or adjustment disorder

- ii. bipolar illness, psychosis, or a family history of these disorders
  - iii. pervasive developmental disorder
  - iv. obsessive-compulsive disorder (OCD)
  - v. psychosis/schizophrenia
  - vi. a serious tic disorder, or a family history of Tourette's disorder
  - vii. Subject is currently considered a suicide risk in the opinion of the investigator, has previously made a suicide attempt, or has a prior history of, or is currently demonstrating active suicidal ideation.
  - viii. a history of physical, sexual, or emotional abuse
  - ix. any other disorder or agitated state that in the opinion of the investigator, contraindicates SPD489 or lisdexamfetamine dimesylate treatment or confound efficacy or safety assessments.
14. Subject has initiated behavioral therapy within 1 month of the baseline visit (Visit 0). Subject may not initiate behavioral therapy during the study.
15. Subject has a height  $\leq$ 5th percentile for age and sex at the screening visit (Visit -1).
16. Subject has a weight  $\leq$ 5th percentile for age and sex at the screening visit (Visit -1).
17. Subject lives with anyone who currently abuses stimulants or cocaine.
18. Subject has a history of seizures (other than infantile febrile seizures).
19. Subject is taking any medication that is excluded per the protocol.

### **4.3 Reproductive Potential**

#### **4.3.1 Female Contraception**

No female subjects in this study are of child bearing potential. All female subjects in this study are pre-menarchal, less than age 9 years, and Tanner Stage 1.

### **4.4 Discontinuation of Subjects**

A subject (parent[s]/LAR) may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time for any reason (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from the clinical study with the medical monitor.

Upon discontinuation of the investigational product, regardless of the reason, the evaluations listed for Visit 6 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination and date of stopping investigational product must be recorded in the case report form (CRF) and source documents.

#### 4.4.1 Management of Blood Pressure and Pulse During the Study

Potential blood pressure and pulse increases must be further evaluated if they meet any of the criteria defined in Sections [4.4.1.1](#) and [4.4.1.2](#).

##### 4.4.1.1 Systolic and Diastolic Blood Pressure

Blood pressure criteria for further evaluation have been developed based on the normative data presented in the National Institutes of Health Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (2004).

Increases in blood pressure (both systolic and diastolic) from the 50th to the 95th percentile (representative of a change of 2 standard deviations) range from 17-20 mmHg for both boys and girls in this age range. Based on this range, an increase of >15 mmHg from the baseline visit (Visit 0) was selected for this protocol.

Prior to obtaining vital signs (blood pressure and pulse) the subject should be at rest for at least 5 minutes.

If any subject's blood pressure measurements meet either criterion below, the investigator will notify the medical monitor. If any subject's blood pressure measurements meet either criterion below on 3 consecutive visits, the subject should be considered for potential discontinuation based upon the clinical judgment of the investigator and in conjunction with the medical monitor.

- Elevations in the average (of 3 readings) sitting systolic blood pressure defined as an increase of >15 mmHg from the baseline visit (Visit 0) OR a value >95th percentile for age, sex, and height
- Elevations in average (of 3 readings) sitting diastolic blood pressure defined as an increase of >15 mmHg from the baseline visit (Visit 0) OR a value >95th percentile for age, sex, and height

##### 4.4.1.2 Pulse

The resting pulse rate criterion for further evaluation has been defined based on the normative data presented in the National Health Statistics Report's "Resting Pulse Rate Reference Data for Children, Adolescents, and Adults: United States, 1999-2008" ([Osthega et al. 2011](#)).

Any subject that has a resting, sitting pulse rate >126 bpm (based on the average of 3 readings) and or is symptomatic requires further assessment. In this case an unscheduled visit needs to be conducted within 1 business day. At the unscheduled visit, if the subject's pulse rate remains >126 bpm (based on the average of 3 readings) or if the subject is symptomatic then the subject's investigator will discuss the findings with the medical monitor. A joint decision between the investigator and the medical monitor will be made regarding continued participation in the study. If a visit cannot be scheduled the next day, the subject may be discontinued from the study.

#### 4.4.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Withdrawal by subject or parent(s)/LAR
- Lost to follow-up
- Lack of efficacy
- Blood pressure and/or pulse criteria met
- Other. If "Other" is selected, the investigator must specify on the CRF

#### 4.4.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject or parent/LAR in the event that any subject is lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

### 5 PRIOR AND CONCOMITANT TREATMENT

All non-study treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy) received within 30 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate CRF page.

#### 5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy) received within 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) prior to the date of first dose of investigational product. Prior treatment information must be recorded on the appropriate CRF page.

The investigator will document that the subject has undergone an adequate course of non-pharmacological treatment or document that the subject has a severe enough condition to consider enrollment without undergoing prior non-pharmacological treatment.

## 5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

### 5.2.1 Permitted Treatment

Medications that may be permitted during the study are listed below. Please consult with the medical monitor:

- Stable (ie, for at least 3 months prior to the screening visit [Visit -1]) dose of thyroid medication is permitted
- Stable (ie, for at least 1 month prior to the screening visit [Visit -1]) dose of bronchodilator inhalers (however, beta-agonists and chronic use of oral corticosteroids is prohibited)
- Any medications that do not affect blood pressure, heart rate, or the CNS, and which are considered necessary for the subject's welfare, may be administered at the discretion of the investigator (eg, antibiotics)
- Non-sedating antihistamines such as fexofenadine (Allegra®, Sanofi), loratadine (Claritin®, Schering-Plough), and cetirizine hydrochloride (Zyrtec®, McNeil-PPC)
- Over-the-counter non-stimulant cold remedies

Concomitant psychotherapy must also be recorded in the appropriate section of the source documents and in the appropriate CRF page.

### 5.2.2 Prohibited Treatment

Table 2 details the washout period, relative to the baseline visit (Visit 0), for treatments that are excluded during this study. Subjects can only be instructed to discontinue a medication for this study after informed consent has been obtained.

**Table 2 Common Excluded Treatments and Associated Washout Period – Relative to Baseline Visit (Visit 0)**

Treatment	Minimum Number of Days Before Baseline Visit		
	7	14	30
Psychostimulants, amphetamines and amphetamine-like agents	X		
Antihypertensives <sup>a</sup>	X		

**Table 2 Common Excluded Treatments and Associated Washout Period – Relative to Baseline Visit (Visit 0)**

Treatment	Minimum Number of Days Before Baseline Visit		
	7	14	30
Antihistamines (centrally and peripherally-active)		X	
Herbal preparations (including melatonin)		X	
Sedatives, anxiolytics, antipsychotics <sup>a</sup>			X
Monoamine oxidase inhibitor (MAOIs) <sup>a</sup>			X
Antidepressants <sup>a</sup>			X
Clonidine and guanfacine			X
Selective noradrenaline reuptake inhibitors and noradrenaline reuptake inhibitors <sup>a</sup>			X
CYP2D6 inhibitors (eg, paroxetine, fluoxetine, quinidine, ritonavir)			X
Alkalinizing agents (eg, sodium bicarbonate, acetazolamide, some thiazides)			X
Acidifying agents (eg, guanethidine, reserpine, glutamic acid HCl, ascorbic acid, ammonium chloride, sodium acid phosphate, methenamine salts)			X

<sup>a</sup> These medications may signal that an exclusionary diagnosis is present. The medical monitor should be consulted prior to instructing a subject to discontinue one of these medications for this study.

## 6 INVESTIGATIONAL PRODUCT

### 6.1 Identity of Investigational Product

The test product is SPD489, which will be provided in 5, 10, 20, and 30 mg capsule form. Additional information is provided in the current SPD489 IB.

The reference/comparator product is placebo which will be provided in matching capsule form.

#### 6.1.1 Blinding the Treatment Assignment

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule. The associated treatment assignments giving details of individual subject treatment are automatically assigned by the Interactive Web Response System (IWRS).

All investigational and reference product will appear identical to protect the study blind.

## **6.2 Administration of Investigational Product(s)**

### **6.2.1 Interactive Response Technology for Investigational Product Management**

An IWRS will be employed in this study to manage the tracking and confirmation of shipments, supply, inventory, ordering, expiration, site assignments, and dosing of the investigational products.

The IWRS provider will provide a user manual and training to each site, with detailed instruction on the use of the IWRS.

### **6.2.2 Allocation of Subjects to Treatment**

This is a randomized, double-blind, fixed-dose, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule. Subjects will be randomized in a 5:5:5:5:6 ratio to SPD489 5, 10, 20, 30 mg or placebo.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

Individual subject treatment is automatically assigned by the interactive web response system (IWRS).

If a randomization number/unique identifier is allocated incorrectly, the clinical research associate (CRA)/study monitor must be notified as soon as the error is discovered.

Investigational product packaging identification numbers, separate from randomization numbers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

### **6.2.3 Dosing**

Dosing should begin at approximately 7:00AM ( $\pm 2$  hours) on the morning after the baseline visit (Visit 0). Subjects will be instructed to take 1 capsule daily in the morning throughout the study, at approximately the same time each day. The same parent/LAR should be available daily to dispense the dose of investigational product for the study duration.

SPD489 may be administered in one of the following ways:

- Swallow SPD489 capsule whole, or
- Open capsule, empty and mix the entire contents with yogurt, water, or orange juice.

The contents should be mixed until completely dispersed. The subject must ingest the entire amount of the mixture immediately within 3 minutes. The subject should not take anything less than one capsule per day and a single capsule cannot be split. The empty gelatinous capsule should be discarded into a trash receptacle by the parent/LAR.

Subjects will begin dosing with the lowest strength of SPD489 (5 mg) and will be titrated until the randomly assigned fixed-dose is reached.

Once subjects reach the fixed-dose level, this dose will be maintained until the end of the study.

No dose reductions are permitted during the study. Subjects who are unable to tolerate investigational product will be discontinued.

#### **6.2.4 Unblinding the Treatment Assignment**

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor as soon as possible after the investigator has been unblinded.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code, are recorded in IWRS and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the contract research organization (CRO) and sponsor. Code-break information is held by the pharmacist/designated person at the site and by the CRO medical monitor for the study or designee.

### **6.3 Labeling, Packaging, Storage, and Handling**

#### **6.3.1 Labeling**

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the protocol number, medication identification number (if applicable), dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference, the statements “For clinical trial use only”, and/or “CAUTION: New Drug - Limited by Federal (or United States [US]) Law to Investigational Use”, “Keep out of reach of children”, and the sponsor's name and address. Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

Space is allocated on the label so that the site representative can record a unique subject identifier and initials.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name.

Additional labels may not be added without the sponsor's prior full agreement.

### **6.3.2 Packaging**

Investigational product is packaged in the following labeled containers:

SPD489 capsules are packaged in 10-count high density polyethylene bottles with child-resistant closures. Each bottle contains a desiccant.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

### **6.3.3 Storage**

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier and initials on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

All controlled-substance investigational product for the sponsor's studies must be stored in a securely locked, substantially constructed room or cabinet according to all applicable local, state, and/or national laws. Limited, controlled access to these investigational products must be maintained, as well as chain of custody, for all investigational product movement.

#### **6.4 Drug Accountability**

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed medication will be documented on the CRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IRT) do not require a shipment form. Returned investigational products must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

## 6.5 Subject Compliance

Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/delegated person will record details on the drug accountability form.

Subjects who have taken 80-100% of the investigational product are regarded as being compliant with the study protocol. Compliance must be assessed by the investigator.

The calculation of medication compliance is as follows:

$$\text{Compliance} = \frac{\text{Total Capsules Taken} \times 100}{\text{Capsules Prescribed by Protocol}}$$

When performing the calculation of medication compliance for investigational product, the total capsules taken must also include number of capsules not returned by the subject to the site.

## 7 STUDY PROCEDURES

### 7.1 Study Schedule

The Schedule of Assessments (Table 1) details all procedures to be completed at each visit and should serve as the primary section of the protocol regarding visit-specific study procedures.

Clinician-completed rating scales and assessments conducted by the site ie, ADHD-RS-IV Preschool Version, CGI-I, and C-SSRS must be completed by the same rater whenever possible.

Throughout the Fixed-dose titration and Dose-maintenance Periods of the study, visits should be scheduled as outlined ( $\pm 3$  days) with reference to the Baseline visit (Visit 0). The Safety Follow-up Call should be scheduled 7 days post-last dose with a +3 day visit window.

Additional unscheduled visits and/or assessments may occur as needed for safety (eg, unscheduled visits for blood pressure and/or pulse measurements will be conducted as described in Section 4.4.1).

#### 7.1.1 Screening and Washout Period

The principal investigator or his/her designee must obtain written informed consent from the subject's parent(s)/LAR prior to any study-related procedures conducted during the screening visit (Visit -1).

There must also be documentation of assent (if required by Institutional Review Board [IRB]), indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to the performance of any study-related procedures.

A washout period may be required to discontinue any prohibited medication (Table 2). A subject cannot be instructed to washout any medication for this study until after informed consent is obtained.

Screening procedures may take place across multiple days to allow enough time to complete all procedures and confirm initial subject eligibility. Screening procedures and dates should be well documented in the source documents and CRF. The date of the screening visit (Visit -1) is the date the parent(s)/LAR and/or subject has signed informed consent for this study.

A screen failure is a subject who has given informed consent and failed to meet any of the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product(s).

For screen failure subjects, the investigator or assigned site staff designee will access the IWRS to record the subject as a screen failure.

Subjects cannot be rescreened once they have been designated as a screen failure. Reassessment of subjects who failed specific inclusion/exclusion criteria is not allowed.

#### **7.1.1.1 Screening Visit (Visit -1)**

Subjects will be screened at Visit -1 to establish eligibility for study participation.

Table 1 details all procedures to be completed at the screening visit (Visit -1). Additional clarification on the procedures performed during the screening visit (Visit -1) is provided below:

- Eligibility will be established per inclusion and exclusion criteria, including documentation of any prior non-pharmacological treatment and specified ADHD and CGI-S severity criteria. Areas of impairment will be recorded for all subjects for assessing the severity of the subject's condition.
- All AEs occurring after signature of informed consent must be recorded in the source documents and CRF.
- Twelve-lead ECG will be performed after 5 minutes of rest. The investigator will perform the initial interpretation of the ECG immediately after collection to ensure the safety of each subject. The ECG tracing will be sent to the central reader for analysis. Upon review of the report from the central reader, the investigator will re-evaluate the clinical significance of the ECG in light of other safety data for the subject. If abnormal and significant results are observed following assessment by the central reader, the investigator, in consultation with the appointed CRO medical monitor, will confirm the subject's eligibility to participate in this study.
- Blood pressure and pulse will be collected after 5 minutes of rest 3 times (with at least 2 minutes in between each collection) using a manual cuff during the visit.

The average of each set of 3 measurements will be used to determine continued participation in the study (see Section 4.4.1).

- BMI should be calculated using one of the following formulae:

$$\text{BMI} = \frac{\text{Weight in pounds} * 703}{(\text{Height in inches})^2}$$

$$\text{BMI} = \frac{\text{Weight in kilograms}}{(\text{Height in meters})^2}$$

- The “Lifetime Recent” version of the Pediatric/Cognitively Impaired Version C-SSRS should be completed.
- Record historical/concomitant medications as follows:
  - All lifetime psychoactive medications and lifetime non-pharmacological interventions (behavioral therapy) for ADHD

#### **7.1.1.2 Other Medications Used During the 30 Days Prior to the Screening Visit (Visit -1) Washout Telephone Call**

The Washout Period should be initiated after clinical laboratory test results and 12-lead ECG results have been received and reviewed by the investigator. Eligible subjects will be contacted by a member of the site staff and provided with instructions on discontinuing any protocol-prohibited medications. During washout, a subject’s current prohibited medications (if applicable) will be discontinued for a period of a minimum of 5 times the half-life of the medication. Washout periods for prohibited medications are defined in [Table 2](#).

As part of the Washout Telephone Call, site personnel should perform the following procedures:

- Schedule the baseline visit (Visit 0)
- Review the inclusion/exclusion criteria
- Ask about any concomitant medications that the subject is taking. If new concomitant medications that require washout are noted, instructions for appropriate washout should be provided.
- Provide instructions on discontinuing any medication requiring washout.
- Determine if any AEs have occurred since the screening visit (Visit -1).

If a medication washout is not necessary, the Washout Telephone Call will include all the above procedures except providing instructions on discontinuing any current medications.

#### **7.1.1.3 Baseline Visit (Visit 0)**

Once the screening central clinical laboratory tests and 12-lead ECG results have been obtained, in addition to repeat assessments (if required), and the subject has completed the required washout period (if applicable), the subject will return to the site for the baseline visit (Visit 0).

Inclusion/exclusion criteria must also be reviewed during this visit to ensure subjects continue to meet all eligibility criteria.

Table 1 outlines all procedures to be conducted during the baseline visit (Visit 0) with further clarification provided below:

- For subjects with more than 30 days since the safety measurements at the screening visit (Visit -1) were collected, an abbreviated physical examination, clinical laboratory tests, and 12-lead ECG must be repeated, and the results reviewed by the investigator prior to the subject being enrolled.
- After 5 minutes rest, blood pressure, and pulse will be collected 3 times (with at least 2 minutes in between each collection) during the visit. The average of each set of 3 measurements will be used to determine continued participation in the study (see Section 4.4.1).
- Three ECGs will be taken, with approximately 5 minutes in between each one, to ensure appropriate baseline intervals are established. The investigator will perform the initial interpretation of the ECG immediately after collection to ensure the safety of each subject to continue with the study. The ECG tracing will be sent to the central reader for analysis. Upon review of the report from the central reader, the investigator will re-evaluate the clinical significance of the ECG in light of other safety data for the subject. If abnormal and significant results are observed following assessment by the central reader, the investigator, in consultation with the appointed CRO medical monitor, will confirm the subject's continued participation in this study.
- The C-SSRS "Since Last Visit" Version of the Pediatric/Cognitively Impaired Version should be completed.
- For eligible subjects, the investigator or assigned site staff designee will access the IWRS to enroll the subject and obtain an investigational product bottle number to dispense to the subject. Subjects will be dispensed a bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule each day. Dosing will begin the morning following the baseline visit (Visit 0).

### **7.1.2 Double-blind Evaluation Periods**

#### **7.1.2.1 Fixed-dose Titration Period (Visits 1 to 3)**

During the first 3 weeks of treatment, visits will be scheduled every 7 days ( $\pm 3$  days) to assess safety, efficacy, and tolerability and to allow investigators to titrate subjects to their randomly assigned fixed-dose strength.

Subjects who are unable to tolerate investigational product should be discontinued from the study.

Throughout the Fixed-dose titration Period, subjects may attend the clinic for unscheduled visits to address any medical needs that arise between scheduled visits.

See [Table 1](#) for procedures that are completed at Visits 1 to 3. Further clarification for these visits is outlined below:

- At each visit during the Fixed-dose titration Period, subjects must return any empty or unused bottles to permit drug accountability and compliance to be assessed.
- Subjects will be dispensed a 10-count bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule each day. Dosing will begin the morning following each visit.
- Blood pressure and pulse will be collected 3 times (with at least 2 minutes in between each collection) during the visit. The average of each set of 3 measurements will be used to determine continued participation in the study (see [Section 4.4.1](#)).
- Scales should be completed by the same rater with input from the same parent/LAR whenever possible.
- The C-SSRS “Since Last Visit” Version of the Pediatric/Cognitively Impaired Version should be completed during the Fixed-dose titration Period.

#### **7.1.2.2 Dose-maintenance Period (Visits 4 to 6)**

Following titration to the randomly assigned fixed-dose strength of SPD489/Placebo, subjects will continue daily morning treatment for an additional 3 weeks.

Throughout the Dose-maintenance Period, subjects may attend the clinic for unscheduled visits to address any medical needs that arise between scheduled visits.

[Table 1](#) outlines the procedures to be completed at each visit during the Dose-maintenance Period. Additional clarification on the procedures to be performed during the Dose-maintenance Period is provided below:

- Scales are to be completed by the same rater with input from the same parent/LAR whenever possible
- At each visit during the Dose-maintenance Period, subjects must return any empty or unused bottles to permit drug accountability and compliance to be assessed.
- Subjects will be dispensed a 10-count bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule each day. Dosing will begin the morning following each visit.
- The C-SSRS “Since Last Visit” Version of the Pediatric/Cognitively Impaired Version should be completed during the Dose Maintenance Period.
- After 5 minutes rest, blood pressure and pulse will be collected 3 times (with at least 2 minutes in between each collection) during the visit. The average of each set of 3 measurements will be used to determine continued participation in the study (see [Section 4.4.1](#)).

### 7.1.2.3 End-of-Study Visit (Visit 6/Early Termination)

All randomized subjects who complete the study or discontinue early will complete Visit 6/early termination (ET).

[Table 1](#) lists the procedures to be completed at Visit 6/ET and should serve as the primary point of reference regarding visit-specific study procedures.

Further clarification on the procedures performed during Visit 6/ET is provided below:

- Unused investigational product and empty containers will be collected to calculate medication compliance.
- After 5 minutes rest, blood pressure and pulse will be collected 3 times (with at least 2 minutes in between each collection) during the visit. The average of each set of 3 measurements will be used to determine continued participation in the study (see [Section 4.4.1](#)).

### 7.1.3 Safety Follow-up Period

The follow-up period for this protocol is 7 days +3 days from the last dose of investigational product.

At the end of this period there will be a telephone call initiated by the site staff to query for serious adverse events (SAEs), AEs, and concomitant treatments. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see [Section 8.1](#)).

### 7.1.4 Additional Care of Subjects After the Study

Subjects who have completed the study at Visit 6 end of study (EOS)/ET may be evaluated for eligibility to enter a long-term safety study of SPD489.

## 7.2 Study Evaluations and Procedures

The individual indicated in each scale description will perform all assessments listed below. Assessments are to be performed according to the schedule shown in [Table 1](#). Care must be taken by the site personnel or the investigator to fully explain the scale prior to completion.

If the subject terminates treatment early, all assessments listed in [Table 1](#) for Visit 6/ET and the Safety Follow-up Call should be completed. Whenever possible, raters (including parent(s)/LAR and the investigator or site designee) observing the subject's behavior should be consistent from visit to visit throughout the study.

### 7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics such as age, sex, weight, height, and BMI will be collected throughout the study according to [Table 1](#).

## **7.2.2 Screening Assessments**

### **7.2.2.1 Kiddie–Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version–Diagnostic Interview**

The sponsor-approved clinician at the site who is trained and experienced in the evaluation of 4- to 5-year-old children with ADHD, will determine a diagnosis of ADHD based on a psychiatric interview and mental status examination utilizing the Kiddie–Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version-Diagnostic Interview (K-SADS-PL) using the DSM-IV-TR criteria for ADHD.

The K-SADS-PL is a semistructured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised and DSM-IV-TR criteria. Probes and objective criteria are provided to rate individual symptoms. The primary diagnoses assessed with the K-SADS-PL include, but are not limited to: major depression, dysthymia, mania, bipolar disorders, schizoaffective disorders, panic disorder, agoraphobia, separation anxiety disorder, avoidant disorder of childhood and adolescence, simple phobia, social phobia, overanxious disorder, generalized anxiety, obsessive compulsive disorder, ADHD, conduct disorder, and oppositional defiant disorder.

The K-SADS-PL is administered by interviewing the parent(s)/LAR(s), the subject, and finally achieving summary ratings, which include all sources of information (parent[s]/LAR, child, school, chart, and other).

The K-SADS-PL will be administered by an individual experienced with the scale and qualified to establish a diagnosis. The site should maintain documentation of the K-SADS-PL training in the site's files. All individuals performing this assessment must be pre-approved by the sponsor or delegated vendor. Based on the above criteria, suitable K-SADS-PL administrators may include physicians, nurse practitioners, or licensed psychologists.

### **7.2.2.2 Peabody Picture Vocabulary Test**

The Peabody Picture Vocabulary Test, Third Edition, measures an individual's receptive (hearing) vocabulary for Standard American English and provides a quick estimate of verbal ability or scholastic aptitude ([Dunn and Dunn 1997](#)). For purposes of this study, the Peabody Picture Vocabulary Test will be used as a proxy for general cognitive ability.

The Peabody Picture Vocabulary Test, Third Edition, should be administered by someone with general knowledge of psychological testing. All individuals performing this assessment must be pre-approved by the Sponsor or designee.

### 7.2.3 Efficacy

#### 7.2.3.1 Attention-deficit/Hyperactivity Disorder Rating Scale – IV Preschool Version

The ADHD-RS-IV Preschool Version ([McGoey et al. 2007](#)), the primary efficacy measure, is completed by the clinician and will be administered at Baseline (Visit 0) and each subsequent visit up to and including Visit 6/ET to capture the ADHD symptoms within each study period. The ADHD-RS-IV Preschool Version was adapted from the ADHD Rating Scale-IV ([DuPaul et al. 1998](#)) and provides examples appropriate for the developmental level of preschool children. The ADHD-RS-IV Preschool Version is an 18-item questionnaire that requires the respondent to rate the frequency of occurrence of ADHD symptoms as defined by DSM-IV-TR criteria. Each item is scored on a 4-point scale ranging from 0 (never or rarely) to 3 (very often) with total scores ranging from 0-54. The 18 items may be grouped into 2 subscales: hyperactivity/impulsivity (even numbered items 2-18) and inattentiveness (odd numbered items 1-17).

The ADHD-RS-IV Preschool Version should be completed by a clinician trained and experienced in the evaluation of preschool children with ADHD. Since the ADHD-RS-IV Preschool Version is used to guide dosing decisions, if it is not completed by the principal investigator or subinvestigator who is medically/clinically responsible for the subject, it must be reviewed and signed by them. All individuals performing this assessment must be pre-approved by the sponsor or designee.

The title, version, and date of the ADHD-RS-IV Preschool Version used in this study are included in [Appendix 3](#).

#### 7.2.3.2 Clinical Global Impressions

The Clinical Global Impressions (CGI) Scale ([Guy 1976](#)) permits a global evaluation of the subject's severity and improvement over time. The CGI has been used extensively in clinical studies of ADHD ([Michelson et al. 2001](#); [Weiss et al. 2005](#); [Wilens et al. 2001](#)).

The investigator will perform the CGI-S to rate the severity of a subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects) at the baseline visit (Visit 0). Additionally, at the baseline visit (Visit 0), the investigator should establish 3 target areas of improvement with the subject and the subject's parent(s)/LAR. To generate the targets, an open-ended question such as, "If this program of treatment works for your child, what things do you hope he/she will be doing better?" should be asked. Ratings will be completed with respect to ADHD symptoms.

At each visit from Visit 1 up to and including Visit 6/ET, the investigator will assess the subject's overall improvement relative to the 3 target areas of improvement recorded at the baseline visit (Visit 0), on the CGI-I, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The CGI-S and CGI-I should be completed by a clinician trained and experienced in the evaluation of preschool children with ADHD. Since the CGI-I is used to guide dosing decisions, if it is not completed by the principal investigator or sub-investigator who is medically/clinically responsible for the subject, it must be reviewed and signed by them. All individuals performing this assessment must be pre-approved by the sponsor or designee.

The title, version, and date of the CGI-S and the CGI-I used in this study are included in [Appendix 3](#).

#### **7.2.4 Safety**

The name and address of each third party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

##### **7.2.4.1 Medical and Medication History**

The investigator will perform a complete medical history at the screening visit (Visit -1), including a medication history, and record all information gathered. The investigator must record all clinically or medically relevant information regardless of how much time has elapsed since the date of diagnosis.

With the subject's parent(s)/LAR's consent, medical records from other treatment providers should be requested.

##### **7.2.4.2 Physical Examination**

A full physical examination will be performed at the screening visit (Visit -1) and Visit 6/ET. Additionally, an abbreviated physical examination is required at the baseline visit (Visit 0) if >30 days have elapsed since the physical examination completed as part of the screening visit (Visit -1) was performed.

A physical examination will be performed by a qualified, licensed individual (eg, physician, physician assistant or a nurse practitioner).

A full physical examination is composed of a review of the following body systems:

- General appearance
- Skin
- Head, Eyes, Ears, Nose, and Throat
- Spine/Neck/Thyroid
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological.

If an abbreviated physical examination is required at the baseline visit (Visit 0), a review of the body systems will include the following:

- General Appearance
- Respiratory
- Cardiovascular.

Abnormalities identified at the screening visit (Visit -1) will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit (Visit -1) will be captured as AEs on the AE CRF page, as deemed by the investigator.

#### **7.2.4.3 Adverse Event Collection**

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (ie, "Have you had any health problems since your last visit, eg, decreased appetite?"). This information should be collected prior to the completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the investigator will be assessed as AEs.

AEs are collected from the time the informed consent is signed. Please refer to Section 8.

#### **7.2.4.4 Vital Signs**

Measurements of oral or tympanic temperature and sitting respiratory rate will be performed at the screening visit (Visit -1) and Visit 6/ET only.

Measurements of sitting systolic and diastolic blood pressure and pulse will be performed at each visit to the site. Blood pressure, pulse, and respiratory rate will be determined after subjects have remained at rest for a minimum of 5 minutes.

Blood pressure will be determined by manual cuff (the same equipment and the same arm should be used throughout the study). A blood pressure cuff appropriate for the subject's arm length and girth should be used for all blood pressure measurements. The cuff should be approximately two-thirds the length/width of the subject's arm (from elbow to shoulder). All blood pressure measurements should be performed throughout the study using a manual cuff and should be performed by the same study center personnel (if possible) throughout the study. After 5 minutes of rest, three measurements should be obtained using the manual cuff with approximately 2 minutes in between each collection for blood pressure and pulse and report the average of the 3 measurements for each parameter. The 3 individual measurements and the averaged reading should be recorded in the source and CRF.

Any clinically significant deviations from Baseline (Visit 0) vital signs which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

#### 7.2.4.5 Height and Weight

Height will be captured at the screening visit (Visit -1) and Visit 6/ET. A calibrated stadiometer must be used for all height measurements. Height should be measured in inches or centimeters without shoes with the subject standing on a flat surface and with chin parallel to the floor. The body should be straight but not rigid.

Weight will be captured at each visit to the site. The same calibrated scale must be used for all weight measurements. Weight should be measured in pounds or kilograms without shoes.

#### 7.2.4.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Clinical laboratory assessments will be performed at the screening visit (Visit -1) and Visit 6/ET. Additionally, clinical laboratory tests are required to be repeated prior to the baseline visit (Visit 0) with results reviewed before enrolling the subject in the study if more than 30 days have elapsed since the clinical laboratory assessments completed as part of the screening visit (Visit -1) were performed. Subjects will have the option of having laboratory assessments collected by a qualified home health care professional at their home. The following clinical laboratory assessments will be performed:

#### Biochemistry and Endocrinology

A blood sample (~5 mL) for biochemistry will be taken to assess the following parameters:

Total Cholesterol	Calcium
Aspartate Transaminase (AST)	Uric Acid
Phosphorus	Blood Urea Nitrogen
Alanine Transaminase (ALT)	Total Bilirubin
Sodium	Creatinine
Alkaline Phosphatase (ALP)	Glucose
Potassium	Albumin
Gamma Glutamyl Transferase (GGT)	Total Protein

TSH Lactate Dehydrogenase

Free T4

### Hematology

A blood sample (~4 mL) for hematology will be taken to assess the following parameters:

Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Red Blood Cells (RBC)	Monocytes
Platelet count	Eosinophils
White Blood Cell (WBC) count – total and differential	Basophils
Mean Corpuscular Hemoglobin (MCH)	Bands
Mean Corpuscular Hemoglobin Concentration (MCHC)	Mean Corpuscular Volume (MCV)

### Urinalysis

A urine sample (~10 mL) for urinalysis will be collected to assess the following parameters:

Glucose	pH
Specific Gravity	Urobilinogen
Blood	Color
Ketones	Leukocyte Esterase
Protein	Nitrate
Bilirubin	

If urinalysis detects protein and/or blood, a microscopic examination will be conducted. The microscopic examination will consist of red blood cell, white blood cell, casts, and bacteria.

#### 7.2.4.7 Electrocardiogram

A 12-lead ECG will be performed at the screening visit (Visit -1) and every post-baseline visit (Visit 1 to Visit 6/ET). Additionally, three ECGs taken approximately 5 minutes apart will be collected at the baseline visit (Visit 0). The mean interval values of the 3 ECGs is used to establish the subject's baseline intervals. All ECGs will be performed after 5 minutes of rest using the central ECG provider's equipment and will be sent to the central ECG provider electronically.

The initial interpretation of the ECG, normal or abnormal, and clinical significance, will be performed immediately after collection by the investigator. The ECG tracing will then be evaluated by a cardiologist at the central ECG reading vendor (Cardiocore) for analysis and returned to the site with a determination of normal or abnormal. Upon review of the report from Cardiocore, the investigator will re-evaluate the clinical significance of the ECG while taking into consideration all other safety data available for the subject.

Although a central ECG reader is being used for this study, the eligibility of the subject is based on the investigator's assessment of the ECG. If abnormal and significant results are observed following assessment by the central reader, the investigator, in consultation with the appointed CRO medical monitor, reconfirms subject eligibility to continue.

All ECGs transmitted to the central ECG reader will be analyzed. If the central ECG reader receives multiple ECGs, the first readable ECGs will be analyzed as the scheduled ECG. Every ECG transmitted to the central ECG reader will have corresponding CRF data collected. No ECG should be deleted by study site personnel. All ECGs must be transmitted to the central provider regardless of quality, results, or number of ECGs taken at a respective visit.

#### **7.2.4.8 Children's Sleep Habits Questionnaire and Sleep Diary**

The Children's Sleep Habits Questionnaire (CSHQ) is a parent report questionnaire designed to screen for the most common sleep problems in children, and consists of 33 items for scoring and several extra items intended to provide administrators with other potentially useful information about respondents. The instrument evaluates the child's sleep based on behavior within 8 different subscales: bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, and daytime sleepiness. The CSHQ will be conducted at each visit to the site starting with the baseline visit (Visit 0) and will be completed by the subject's parent(s)/LAR.

The subject's parent(s)/LAR will complete a sleep diary to log daytime napping, bedtime, and wake time.

#### **7.2.4.9 Columbia-Suicide Severity Rating Scale**

The C-SSRS ([Posner 2007](#)) is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The C-SSRS contains 2 required items pertaining to suicidal ideation, 4 required items pertaining to suicidal behavior, and 1 required item pertaining to non-suicidal but self-injurious behavior. In situations where there is a positive response to the screening questions, there are 8 additional suicidal ideation items and 4 additional suicidal behavior items which are completed. Thus, there is a maximum of 19 items to be completed.

The C-SSRS must be performed by an individual who is trained and certified and is preapproved by the sponsor or delegated vendor and the site investigator.

The Pediatric/Cognitively Impaired Version of the scale will be used in the study. Two time point versions of the C-SSRS are used in this study:

- The “Lifetime Recent” version will be administered at the screening visit (Visit -1).
- The “Since Last Visit” version will be completed at all study visits after the screening visit (Visit -1).

The title, version, and date of the C-SSRS “Lifetime Recent” version and the C-SSRS “Since Last Visit” version used in this study are included in [Appendix 3](#).

#### 7.2.4.10 Suitability of the Subject to Remain in the Study

At each visit (except for Visit 6/ET) starting with the baseline visit (Visit 0), the investigator will assess the subject’s ability to continue in the study. The investigator or a medically qualified designee will review all available safety information (including weight and BMI) and will evaluate for the presence of decreased appetite potentially leading to weight loss. In cases where the subject has clinically significant decrease in appetite, the investigator should intervene as necessary based on clinical judgment (eg, diet/behavioral interventions) and consider discontinuation of treatment if necessary. In cases where the subject has had  $\geq 7\%$  weight loss the investigator must discuss the case with the medical monitor and assess whether it’s in the best interest for the subject to remain in the study.

As part of the assessment of the subject’s suitability to remain in the study the investigator should also assess the subject’s current potential for suicide, suicidal ideation, self-harm, or harm to others, as well as psychiatric disorders. The investigator should make this assessment by conducting a clinical interview with the subject and by reviewing of all other relevant sources available, including results of the C-SSRS. Any subject who has 1 or more positive responses must undergo further evaluation to ensure that they are not in any way at risk. As part of this assessment, if appropriate, the investigator should discuss risk factors for suicide with the subject. Where a subject has suffered an accidental injury, the investigator should ensure that this was a true accidental injury, rather than an episode of self-harming or a suicide attempt.

The subject’s source notes should clearly document that the assessment of continued suitability including assessment of the subject’s appetite, weight loss and current potential risk of suicide, suicidal ideation, feelings of hopelessness, drug use, self-harm, or harm to others has taken place and should contain the decision on whether the subject is suitable to continue in the study.

#### 7.2.4.11 Volume of Blood to be Drawn From Each Subject

**Table 3** Volume of Blood to be Drawn From Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety	Biochemistry	5	2	10
	Hematology	4	2	8
Total mL				18

During this study, it is expected that approximately 18 mL of blood will be drawn from all subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 18 mL. When more than 1 blood assessment is to be done at the timepoint/period, if they require the same type of tube, the assessments may be combined. If a catheter is used, the first 1 mL of blood from each sampling will be discarded. Biochemistry and hematology clinical laboratory tests will be repeated at the baseline visit (Visit 0) if >30 days have elapsed since the screening visit (Visit -1).

## **8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT**

### **8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events**

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that 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 temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

#### **8.1.1 Severity Categorization**

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

**Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

**Moderate:** A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

**Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

### 8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as “not related”. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related”. The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject’s medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject’s underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

### 8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown.

#### 8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

#### 8.1.5 Clinical Laboratory and Other Safety Evaluations

Clinical laboratory assessments, vital sign, and ECG assessments are performed at the Screening Visit (Visit 1) and Visit 6/ET. The investigator is required to review these assessments prior to determining subject eligibility. A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant, and therefore represents an AE.

#### 8.1.6 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol.)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 30 mg of the product.

- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The dispensing, administration, and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent(s)/LAR/caregiver.

## **8.2 Serious Adverse Event Procedures**

### **8.2.1 Reference Safety Information**

The reference for safety information for this study is the IB which the sponsor has provided under separate cover to all investigators.

### **8.2.2 Reporting Procedures**

All initial and follow-up SAE reports must be reported by the investigator to the Shire Pharmacovigilance Department ([GlobalPharmacovigilance@shire.com](mailto:GlobalPharmacovigilance@shire.com)) and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.6) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Trial Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Pharmacovigilance Department. A copy of the Shire Clinical Trial Serious Adverse Event Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the [emergency contact information](#) section of the protocol.

### **8.2.3 Serious Adverse Event Definition**

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).

- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. 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; or the development of drug dependency or drug abuse.

#### **8.2.4 Serious Adverse Event Collection Timeframe**

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

#### **8.2.5 Serious Adverse Event Onset and Resolution Dates**

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

#### **8.2.6 Fatal Outcome**

Any SAE that results in the subject’s death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject’s death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject’s death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as “dose not changed” or “not applicable” (if the subject never received investigational product).

### **8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting**

The sponsor and the clinical CRO are responsible for notifying the relevant regulatory authorities and US central IRBs of related, unexpected SAEs.

In addition the sponsor and clinical CRO are responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SPD489 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

## **9 DATA MANAGEMENT AND STATISTICAL METHODS**

### **9.1 Data Collection**

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

### **9.2 Clinical Data Management**

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

### **9.3 Data Handling Considerations**

Data that may potentially unblind the treatment assignment (ie, treatment and bottle allocation) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

## 9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS<sup>®</sup> (SAS Institute, Cary, NC 27513) and R MCP-Mod package.

## 9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

### 9.5.1 Interim Analysis

The study implements a group sequential design with one interim analysis. The interim analysis is proposed when approximately 60% of planned subjects who either complete or discontinue the study.

The interim analysis will be conducted on the interim analysis dataset, which is defined as all data from 60% of initially planned subjects who have either completed or discontinued the study, together with data for subjects who are in the study up to the interim analysis data cut time point. The efficacy, safety, and sensitivity on missing data mechanisms analyses at the interim analysis will primarily be conducted using this dataset.

The Lan-DeMets alpha spending function with O'Brien-Fleming boundary will be used for alpha spending between the interim and EOS analysis for the primary efficacy endpoint. Following evaluations in the stage-wise hierarchical setting ([Glimm et al. 2010](#)), the Lan-DeMets alpha spending function with Pocock boundary will be applied to analyze the key secondary efficacy endpoint. This approach will strongly control the study-wide type I error at the overall 0.05 significance level, and in general increase power for the test on the key secondary endpoint.

If the hypothesis for the primary efficacy endpoint is rejected at the interim analysis, then the study will be stopped for efficacy and all ongoing subjects from the study (SPD489-347) will be immediately rolled over to the open-label extension study (Study SPD489-348). In this case, using the same data cut point that contains the same information fractions as the primary efficacy interim analysis, the key secondary efficacy endpoint will be tested. In addition, the incremental data collected during the interim analysis process, i.e., the overrun, together with the interim analysis dataset will be utilized in sensitivity analyses for major efficacy and safety end points. Otherwise, if the primary efficacy criterion is not met at the interim analysis, then the hypothesis for the key secondary endpoint will not be tested at this time, and the study will continue to its completion, then the primary efficacy endpoint will be tested.

If the primary efficacy test is rejected, then the key secondary efficacy endpoint will be tested. This testing procedure strongly protects the overall alpha level. In addition, all other efficacy and safety analyses will be conducted at this time.

At the interim or final efficacy analysis, only the primary efficacy result will be used to determine if the study meets the efficacy criterion. The nominal significance level for the interim or final primary and key secondary efficacy endpoints for a 2-sided at a 0.05 significant level are specified below, calculated using East<sup>®</sup> 6.4. The calculations are based on 60% of planned sample size, and will be updated based on the actual information fraction at the interim analysis.

	Efficacy Boundary p-value Scale	
	Interim Analysis	Final Analysis
Primary Endpoint	0.0074	0.0477
Key Secondary Endpoint	0.0354	0.0257

If the primary efficacy criterion is not met at the interim analysis, and the blinded sample size re-estimation causes a sample size increase, the nominal significance levels at the end of the study will be recalculated such that the overall alpha level is not greater than 0.05 for the primary and key secondary analyses together. The calculations will be based on the new increased sample size, the actual information ratio, and the alpha already spent.

It is estimated that the interim analysis will take up to 8 weeks from data cutoff to its completion. If the recruitment rate is high and the remaining 40% planned subjects are projected to be all or nearly all enrolled within those 8 weeks, the interim analysis will be waived with reasons documented. In this case, the EOS analysis will be conducted at the 2-sided significance level of 0.05 with primary and key secondary endpoints tested sequentially.

Separately, if the primary efficacy criterion is met at the interim analysis, the interim analysis dataset together with overrun data will be used to evaluate the dose-response relationship with the Dose Response Analysis Set (DRAS). If the primary efficacy criterion is not met at the interim analysis and study continues to its completion, dose-response evaluation will be conducted using the EOS data.

### 9.5.2 Sample Size Re-estimation

In order to maintain sufficient study power to detect a clinically meaningful treatment effect for the primary efficacy endpoint, a blinded sample size re-estimation is planned. If the study continues beyond the proposed interim analysis, or if the interim analysis is waived, then the sample size re-estimation will be performed when approximately 75% of the 195 subjects have either completed or discontinued from the study. In this case, cumulative primary efficacy data will be used to estimate a pooled common standard deviation (SD) to ensure the variability hypothesized at the design stage is not underestimated.

Together with the assumed treatment difference of 8.4, the final total number of subjects to be enrolled will be calculated using the re-estimated pooled SD (Friede and Kieser 2006).

The final total sample size could potentially be as high as 218 completers, which corresponds to the 97.5% percentile of the distribution of the estimator on the assumed true common SD of 14 postulated at the design stage. If the re-estimated pooled common SD is larger than 14, the sample size will be increased. Otherwise, the sample size will remain the same. Note that the total of 218 completers is not considered a cap. As the final sample size is data driven, a higher number, though unlikely, is possible.

The Type-I error level for the sample size re-estimation will be adjusted based on the O'Brien-Fleming boundary when applicable.

### 9.5.3 Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) was set up to review the data pertaining to safety, tolerability, and benefit/harm of the study therapy for the duration of this Pediatric Written Request program, which includes studies SPD489-211, SPD489-347, and SPD489-348. The same DMC will evaluate the efficacy analysis results and supportive safety summaries to determine if the interim efficacy criteria are met for this study. Confidentiality of the unblinded DMC analyses is a critical concern and to address this, an unblinded independent reporting team will be identified within a CRO. The independent reporting team will have no involvement in the conduct of the study. Further details regarding the DMC can be found in the DMC charter.

The DMC will not be involved in the blinded sample size re-estimation and dose-response relationship evaluations.

### 9.6 Sample Size Calculation and Power Considerations

Approximately 195 subjects will be randomized in a 5:5:5:5:6 ratio to SPD489 5, 10, 20, 30 mg or placebo to achieve 156 completers for the study (30 in each active treatment group and 36 in the placebo group) and 85% power for the primary efficacy analysis at a 2-sided 0.05 significance level. The sample size planned at study initiation is estimated based on the primary comparison between pooled SPD489 10, 20, and 30 mg dose levels (excluding the 5 mg) and placebo on the primary efficacy endpoint, in a group sequential design with 1 interim analysis using the Lan-DeMets alpha spending function with O'Brien-Fleming boundary for the primary efficacy endpoint. Assumptions for the calculation include the true mean difference of 8.4 with the common standard deviation (SD) of 14 for the primary efficacy endpoint, for an effect size of 0.6, and a dropout rate of 20%.

The dose-response relationship that measured as the ADHD-RS-IV Preschool Version Total Score change from baseline will be evaluated separately. Assuming the maximum difference in change from baseline in ADHD-RS-IV Preschool Version Total Score between 0 mg (placebo) and SPD489 (5, 10, 20 or 30 mg) is 13.0 points, and has a standard deviation of 14 for the change, then in order to detect a plausible dose-response curve at 85% power and a significance level of 0.05 (2-sided) using MCP-Mod with equal allocation to the treatment groups, it is necessary to have 18 completers for each arm.

Assuming a 20% dropout rate, a total of 24 subjects for each treatment group are required to be randomized. Therefore, the overall sample size of the study will be sufficient for dose-response analysis.

## 9.7 Study Population

The **Screened Set** will consist of all subjects who have signed an informed consent.

The **Randomized Set** will consist of all subjects in the Screened Set for whom a randomization number has been assigned.

The **Safety Analysis Set** will consist of all subjects in the Randomized Set who have taken at least 1 dose of investigational product.

The **Full Analysis Set** (FAS) will consist of all subjects in the Safety Analysis Set who have at least 1 post baseline ADHD-RS-IV Preschool Version Total Score assessment, where baseline is defined as the last valid assessment prior to taking the first dose of investigational product.

The **Dose Response Analysis Set** (DRAS) will consist of all subjects in the Safety Analysis Set who have at least 1 valid primary efficacy measurement (ADHD-RS- IV Preschool Version Total Score) on the randomized target dose level of the investigational product.

The above analysis sets are similarly defined for both the interim and the complete study analyses.

## 9.8 Efficacy Analyses

The primary and key secondary analyses, including sensitivity analyses, will be based on the FAS and will be conducted on either the interim analysis dataset or all cumulative data up to study completion, whenever it is appropriate. Specifically, these analyses will compare between placebo and pooled SPD489 10, 20, 30 mg dose strengths together, excluding the 5 mg arm. For primary and key secondary endpoints, statistical tests are planned to control the study-wide type I error at the 2-sided 5% level, as described in Section 9.5. All other statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance, with no adjustment for multiplicity. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. In addition, the dose response relationship evaluations will be performed over the DRAS and using appropriate datasets. For this case, all randomized investigational product groups, which include 0 (placebo), 5, 10, 20, 30 mg (SPD489) doses will be used.

Rules for missing data handling will be described in the SAP.

### 9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the change from baseline in clinician-administered ADHD-RS-IV Preschool Version Total Score at Visit 6 (Week 6).

The statistical hypotheses of the primary efficacy analysis are:

- The null hypothesis is: there is no treatment difference between pooled SPD489 (10, 20, and 30 mg) dose group and placebo at Visit 6 (Week 6)
- The alternate hypothesis is: there is a difference between pooled SPD489 (10, 20, and 30 mg) dose group and placebo at Visit 6 (Week 6).

The estimand of primary interest is:

Estimate of the average effect attributable to the experimental treatment as compared to placebo at Visit 6 (Week 6), for all subjects in the FAS of the study.

The primary efficacy endpoint will be analyzed using the linear mixed-effects model for repeated measures (MMRM). The analysis includes the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, the covariate of baseline ADHD-RS-IV Preschool Version Total Score, and with the baseline ADHD-RS-IV Preschool Version Total Score-by-visit interaction adjusted in the model. The primary contrast of interest will be pooled 10, 20, and 30 mg treatment effect at Visit 6 (Week 6) for SPD489 compared with placebo. Missing data will not be imputed.

Sensitivity analysis on missing data for the primary efficacy endpoint will be described in the SAP.

### **9.8.2 Key Secondary Efficacy Endpoints**

The key secondary efficacy endpoint CGI-I provides an overall assessment of global symptom improvement. It will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The baseline CGI-S score will be used as the covariate. The contrast of interest will be at Visit 6 (Week 6) for SPD489 compared with placebo.

### **9.8.3 Secondary Efficacy Endpoints**

The primary and key secondary efficacy analyses, and dose-response analysis will be conducted separately, and therefore no multiplicity adjustment will be considered for these objectives together.

Using a pre-specified set of candidate dose-response curves that are selected based on prior knowledge of SPD489 dose-response and assumptions on fixed-doses effects (placebo, SPD489 5, 10, 20, and 30 mg), the dose-response relationship of SPD489 as measured by the change from baseline for ADHD-RS-IV Preschool Version Total Score will be evaluated using the DRAS. The MCP-Mod methodology will be used to identify the optimized dose-response curve and the minimum effective dose (MED).

The assumed family of plausible dose-response curves consists of linear,  $E_{max}$ , and logistic relationships, with appropriate parameters, covering the dose ranges of 0 mg (placebo) to 30 mg of investigational product. When the study completes, regardless at the interim analysis or at end of the study, using all cumulative available data, the dose-response relationship of SPD489 as measured by the change from baseline for ADHD-RS-IV Preschool Version Total Score fitting with a candidate curve will be evaluated.

## 9.9 Safety Analyses

The Safety Analysis Set based on either the interim analysis dataset or all cumulative data up to study completion, whenever it is appropriate, will be used to report the safety data.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and visit using appropriate descriptive statistics. Potentially clinically important findings will also be summarized by treatment group and listed.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. TEAEs are defined as AEs that start or deteriorate on or after the date of the first dose of investigational product and no later than 3 days following the last dose of investigational product in the double-blind phase.

Treatment-emergent AEs will be summarized. The number and percent of subjects with TEAEs will be calculated for each system organ class, by preferred term, and by treatment. The severity of the TEAEs, the relationship to the investigational product, TEAEs causing study discontinuation, serious AEs and death will also be presented.

The CSHQ will be summarized by treatment group using appropriate descriptive statistics at each visit.

Sleep diary data will be descriptively summarized by treatment group.

A summary and listing of the C-SSRS data will be provided for subjects with a positive response only.

## 10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

### 10.1 Sponsor's Responsibilities

This study is conducted in accordance with current applicable regulations, ICH and any updates or revisions, and local ethical and legal requirements.

The name and address of each third party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

#### 10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996) and any updates or revisions, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

#### **10.1.2 Public Posting of Study Information**

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

#### **10.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees**

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

#### **10.1.4 Study Suspension, Termination, and Completion**

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

### **10.2 Investigator's Responsibilities**

#### **10.2.1 Good Clinical Practice Compliance**

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and any updates or revisions, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time, resources, and appropriately trained personnel are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study).

### **10.2.2 Protocol Adherence and Investigator Agreement**

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

### **10.2.3 Documentation and Retention of Records**

#### **10.2.3.1 Case Report Forms**

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

#### **10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents**

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diary cards and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.)

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

#### **10.2.3.3 Audit/Inspection**

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, eg, the US FDA (as well as other US national and local regulatory authorities), other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

#### **10.2.3.4 Financial Disclosure**

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54.2(b) (1998).

#### **10.2.4 Compliance to all Local, State, and National Controlled-substance Biohazard and Infectious Disease Regulations and Legislation**

When using controlled substances, the investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

### **10.3 Ethical Considerations**

#### **10.3.1 Informed Consent**

It is the responsibility of the investigator to obtain written informed consent and assent from all study subjects prior to any study-related procedures including screening assessments. Subject's parent(s) or LAR must provide signature of informed consent, and there must be documentation of assent (if applicable) by the subject in accordance with the International Council on

Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996), any updates or revisions, and applicable regulations, before completing any study related procedures. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject, parent or the subject's LAR, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject, parent, or LAR has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's LAR, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Within the source documents, site personnel should document instruction of and understanding by the parent(s)/LAR/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form and assent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

### **10.3.2 Institutional Review Board or Ethics Committee**

It is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the CRO has received written IRB/EC approval of and copies of revised documents.

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

#### **10.4 Privacy and Confidentiality**

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor, and/or its representative's reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SPD489; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

#### **10.5 Study Results/Publication Policy**

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications.

To the extent that the principal investigator has such sole, joint, or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term “publication” refers to any public disclosure including original research articles, review articles, oral presentations, abstracts, and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor’s confidential information shall be submitted for publication without the sponsor’s prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor’s presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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**12 APPENDICES**

**APPENDIX 1 PROTOCOL HISTORY**

Document	Date	Global/Country/Site Specific
Original Protocol	01 August 2016	Global
Amendment 1	23 February 2017	Global
Amendment 2	05 June 2017	Global
Amendment 3	04 August 2017	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
2	05 Jun 17	Global
Section	Description of Change	
Global change	Changed flexible dose study design to a fixed-dosed design, based on FDA feedback. Subjects will be dose-titrated to randomized, assigned dose rather than dose-optimized to optimal dose	
Synopsis, Section 3.1, Section 6.2.2.2 (deleted from previous version.)	Secondary endpoint to evaluate PK was removed.	
Synopsis, Section 3.1, Schedule of Assessments	Dose-titration period will be 3 weeks rather than 4 weeks reducing the total treatment period to 6 weeks rather than 8 weeks	
Synopsis, Section 3.1	Sample size increased to approximately 245 screened subjects to randomize approximately 195 subjects to achieve 156 completers in a 5:5:5:5:6 ratio of SPD489 to placebo (30 in each active treatment dose group and 36 in the placebo group)	
Synopsis, Section 3.3	Change from 50 to 60 sites	
Synopsis, Section 2.2.2, Section 9.8.3	Added a secondary efficacy endpoint to evaluate the dose response relationship of SHP489 for randomized fixed-doses strength (placebo, SHP489 5, 10, 20, and 30 mg), as measured by the change from baseline for ADHD-RS Preschool Version Total Score at study stop (at interim analysis or end of study).	
Synopsis, Schedule of Assessments, Section 2.2.2, Section 7.1.2.2, Section 7.2.4.11, Removed Section 7.2.5, Section 9.10, Appendix 4	Removed pharmacokinetic (PK) sampling and analysis. Removed the secondary objective and endpoint to evaluate PK and explore exposure-response relationship in preschool children with ADHD.	
Synopsis, Section 4.2	Clarified exclusion criterion:  13. Subject has a current, controlled (requiring medication or therapy) or uncontrolled, co-morbid psychiatric disorder including but not limited to any of the below co-morbid Axis I disorders and Axis II disorders:	

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
2	05 Jun 17	Global
Section	Description of Change	
	i. post-traumatic stress disorder or adjustment disorder ii. bipolar illness, psychosis, or family history of these disorders	
Synopsis, Section 9.4, Section 9.5.1, Section 9.6	Description of additional information and changes regarding the interim and final analysis	
Synopsis, Section 9.5.2	Clarification regarding sample size re-estimation	
Section 5.2.1	Added consultation with medical monitor regarding permitted treatment/medications and added (eg, antibiotics) as clarification to the "Any medications..." bullet	
Section 7.1.1.3, Section 7.1.2.2, Section 7.1.2.3	Added details regarding blood pressure and pulse measurements	
Section 7.2.4.7	Clarification of ECG details and addition of Cardiacore as central ECG reading vendor.	
Section 7.2.4.11	Decrease in blood volume to be collected since PK samples are no longer be collected	

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	23 Feb 17	Global
Section	Description of Change	
Abbreviations	Updated to reflect changes described in this table.	
Synopsis, Section 7.1.2, Section 7.2.5, Section 9.7, Section 9.10	Additional secondary endpoint was added: • To evaluate PK and explore exposure-response relationship in preschool children with ADHD. Associated assessments were added.	
Table 1	Updated to reflect changes described in this table	
Synopsis and Section 2.1	Updated based on results from Study SHP489-211	
Synopsis, Section 3.1, Section 7.2, Section 9.8	Study length changed to 8 weeks	
Synopsis, Section 4.2 and Section 7	Exclusion criteria were changed: • Subject has a blood pressure measurement $\geq 95$ th percentile for age, sex, and height at the screening visit (Visit -1) or the baseline visit (Visit 0) or a history of moderate or severe hypertension.	

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number	Amendment Date	Global/Country/Site Specific
1	23 Feb 17	Global
Section	Description of Change	
	<ul style="list-style-type: none"> <li>• Subject has a known history of symptomatic cardiovascular disease, unexplained syncope, exertional chest pain, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems placing them at increased vulnerability to the sympathomimetic effects of a stimulant drug.</li> <li>• Subject has a history of hyperthyroidism, or current abnormal thyroid function, defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4) at the screening visit (Visit -1). Treatment with a stable dose of thyroid medication for at least 3 months is permitted.</li> <li>• Subject has a current, controlled (requiring medication or therapy) or uncontrolled, co-morbid psychiatric disorder including but not limited to any of the below co-morbid Axis I disorders and Axis II disorders:               <ul style="list-style-type: none"> <li>• any other disorder or agitated state that in the opinion of the investigator, contraindicates SPD489 or lisdexamfetamine dimesylate treatment or confound efficacy or safety assessments.</li> </ul> </li> </ul>	
Section 4.4.1.1, 7.1.1.1	Systolic and Diastolic Blood Pressure details of assessment have been added.	
Section 4.4.1.2, 7.1.1.1	Pulse details of assessment have been added.	
Synopsis, Section 6.1, 6.2.3, 7.1.2	Dosing information updated based on results from Study SHP489-211	
Section 9.5.1	Nominal significance level changed to 0.0308.	

## APPENDIX 2 DIAGNOSTIC CRITERIA/DISEASE CLASSIFICATION

### APPENDIX 2.1 DSM-IV-TR CRITERIA FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A. Either (1) or (2):

- (1) six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

*Inattention*

- (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
  - (b) often has difficulty sustaining attention in tasks or play activities
  - (c) often does not seem to listen when spoken to directly
  - (d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
  - (e) often has difficulty organizing tasks and activities
  - (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
  - (g) often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)
  - (h) is often easily distracted by extraneous stimuli
  - (i) is often forgetful in daily activities
- (2) six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

*Hyperactivity*

- (a) often fidgets with hands or feet or squirms in seat
- (b) often leaves seat in classroom or in other situations in which remaining seated is expected
- (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- (d) often has difficulty playing or engaging in leisure activities quietly
- (e) is often “on the go” or often acts as if “driven by a motor”
- (f) often talks excessively

*Impulsivity*

- (g) often blurts out answers before questions have been completed
  - (h) often has difficulty awaiting turn
  - (i) often interrupts or intrudes on others (eg, butts into conversations or games)
- B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
- C. Some impairment from the symptoms is present in 2 or more settings (eg, at school [or work] and at home).
- D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
- E. The symptoms do not occur exclusively during the course of a Pervasive Development Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (eg, Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

*Code based on type:*

**314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type:**

if both Criteria A1 and A2 are met for the past 6 months

**314.00 Attention-Deficit/Hyperactivity Disorder, Predominately Inattentive Type:**

if Criterion A1 is met but Criterion A2 is not met for the past 6 months

**314.01 Attention-Deficit/Hyperactivity Disorder, Predominately Hyperactive-Impulsive Type:** if Criterion A2 is met but Criterion A1 is not met for the past 6 months

*From the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Copyright 1994 American Psychiatric Association*

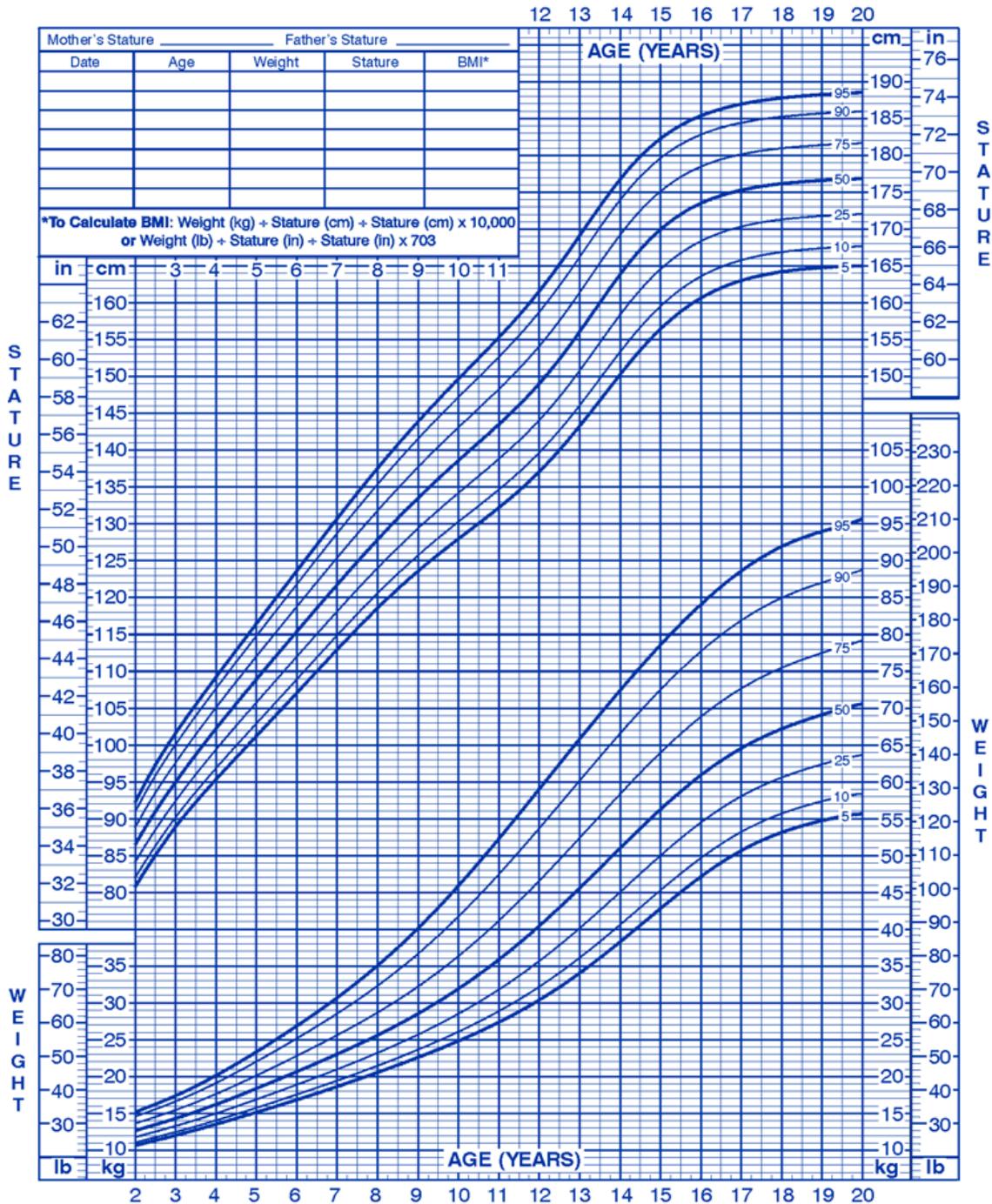
**APPENDIX 2.2 BOYS' STATURE-FOR-AGE AND WEIGHT-FOR-AGE PERCENTILES**

2 to 20 years: Boys

NAME \_\_\_\_\_

Stature-for-age and Weight-for-age percentiles

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



**APPENDIX 2.3 BLOOD PRESSURE LEVELS FOR BOYS BY AGE AND HEIGHT PERCENTILE**

To determine the eligibility of a male subject for entry in the study (based on the study inclusion criteria), first determine the percentile of height for the subject based on their age (as a whole number based on the subject’s last birthday; see the Boys’ Stature-for-age and Weight-for-age Percentiles). For subjects who fall between the 2 height percentiles, use the lower of the 2 percentiles. Once the subject’s age and height percentile for age are determined, use the table below to determine eligibility.

All blood pressure values listed below are 95th percentile for age and height percentile. The subject’s systolic and diastolic blood pressure readings at the Screening Visit (Visit -1) and the Baseline Visit (Visit 0) must not exceed the corresponding table value below for their age and height percentile.

Age (Year)	Systolic Blood Pressure (mmHg)							Diastolic Blood Pressure (mmHg)						
	← Percentile of Height →							← Percentile of Height →						
	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
4	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	108	109	110	112	114	115	116	60	70	71	72	73	74	74
6	109	110	112	114	115	117	117	72	72	73	74	75	76	76

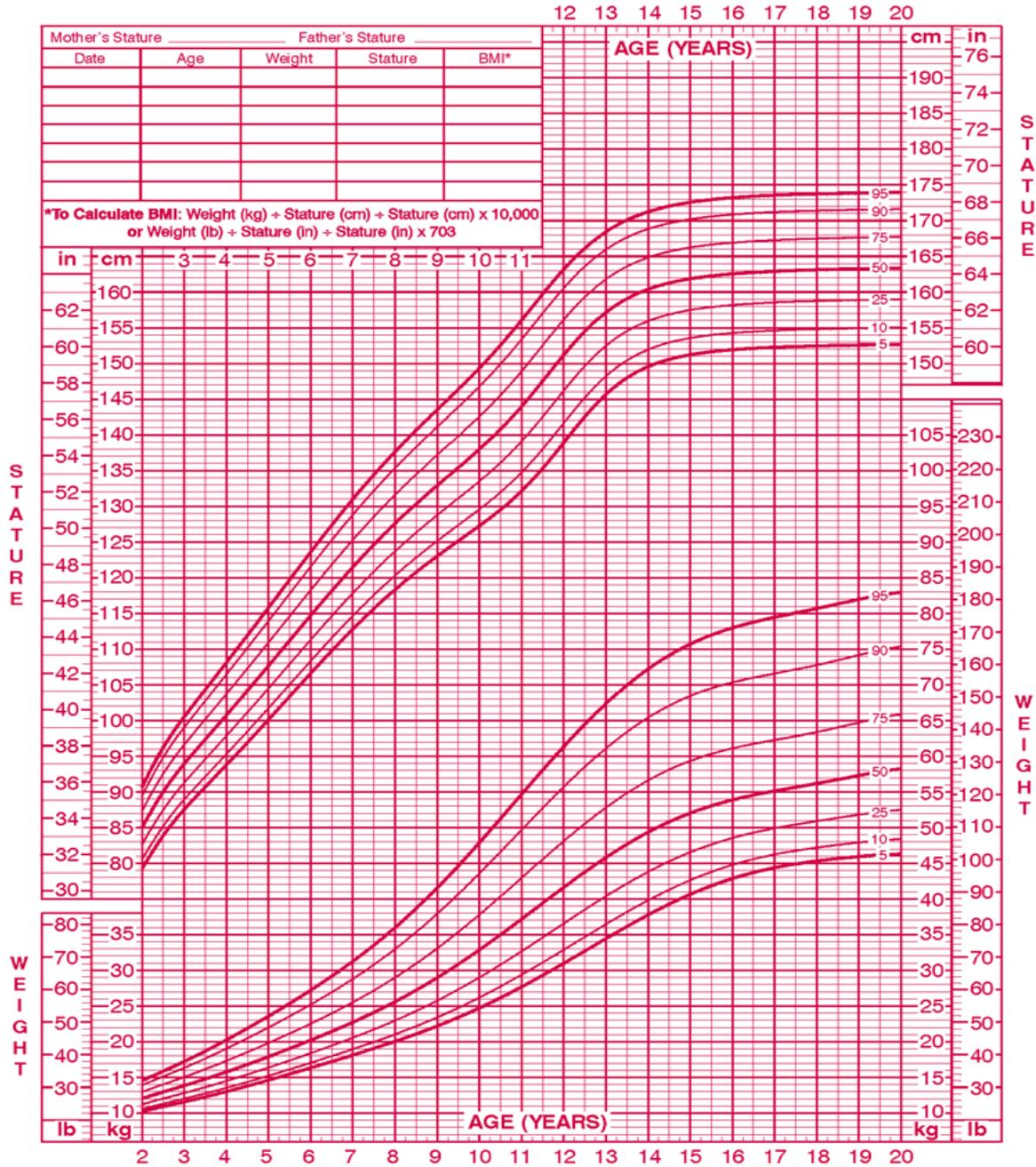
Source: National Heart Lung and Blood Institute; May 2004  
[http://www.nhlbi.nih.gov/guidelines/hypertension/child\\_tbl.htm](http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm)

**APPENDIX 2.4 GIRLS' STATURE-FOR-AGE AND WEIGHT-FOR-AGE PERCENTILES**

**2 to 20 years: Girls**  
**Stature-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



**APPENDIX 2.5 BLOOD PRESSURE LEVELS FOR GIRLS BY AGE AND HEIGHT PERCENTILE**

To determine the eligibility of a female subject for entry in the study (based on the study inclusion criteria), first determine the percentile of height for the subject based on their age (as a whole number based on the subject’s last birthday; see the Girls’ Stature-for-age and Weight-for-age Percentiles). For subjects who fall between the 2 height percentiles, use the lower of the 2 percentiles. Once the subject’s age and height percentile for age are determined, use the table below to determine eligibility.

All blood pressure values listed below are 95th percentile for age and height percentile. The subject’s systolic and diastolic blood pressure readings at the Screening Visit (Visit -1) and the Baseline Visit (Visit 0) must not exceed the corresponding table value below for their age and height percentile.

Age (Year)	Systolic Blood Pressure (mmHg)							Diastolic Blood Pressure (mmHg)						
	← Percentile of Height →							← Percentile of Height →						
	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
4	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	108	109	110	111	113	114	115	72	72	73	74	74	75	76

Source: National Heart Lung and Blood Institute; May 2004  
[http://www.nhlbi.nih.gov/guidelines/hypertension/child\\_tbl.htm](http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm)

### APPENDIX 3 SCALES AND ASSESSMENTS

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Version Number	Date Issued
ADHD Rating Scale – IV Preschool Version	N/A	2007
Clinical Global Impressions – Global Improvement and Clinical Global Impressions – Severity of Illness	N/A	1976
Columbia-Suicide Severity Rating Scale	Lifetime Recent Since Last Visit	Lifetime Recent 6/23/10 Since Last Visit 6/23/10
Peabody Picture Vocabulary Test	3 <sup>rd</sup> Edition	1997
Kiddie–Schedule for Affective Disorders and Schizophrenia for School-age Children– Present and Lifetime Version–Diagnostic Interview	1.0	1996
ADHD Rating Scale – IV Preschool Version (Teacher)	N/A	2007
Children’s Sleep Habits Questionnaire	N/A	2009

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.