PROTOCOL: SPD489-348

TITLE: A Phase 3, Open-label, Multicenter, 12-Month Safety and Tolerability Study of SPD489 in Preschool Children Aged 4-5 Years Diagnosed with Attention-deficit/Hyperactivity Disorder

DRUG: SPD489, Lisdexamfetamine dimesylate

IND: 67,482

EUDRACT NO.: Non EUDRACT

SPONSOR:

Shire Development LLC and International Affiliates
725 Chesterbrook Boulevard, Wayne, PA 19087 USA

PRINCIPAL/ COORDINATING INVESTIGATOR: [redacted] USA

PROTOCOL HISTORY: Original Protocol: 21 Oct 2014

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

[redacted]	D[redacted]
	{[redacted] *not precede the approval date}*

Investigator's Acknowledgement

I have read this protocol for Shire Study SPD489-348.

Title: A Phase 3, Open-label, Multicenter, 12-Month Safety and Tolerability Study of SPD489 in Preschool Children Aged 4-5 Years Diagnosed with Attention-deficit/Hyperactivity Disorder (ADHD)

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 Conference on 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:** _____

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Trial Serious Adverse Event Form within 24 hours to the Shire Pharmacovigilance Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of the Shire Clinical Trial Serious Adverse Event Form must also be sent to the CRO/Shire Medical Monitor by fax or e-mail using the details below.

Fax: [redacted]

E-mail address: [redacted] (electronic query submission site)

For protocol- or safety-related issues <u>during normal business hours 8AM-5PM eastern standard time</u>, the investigator must contact the PPD Medical Monitor:

[redacted]

Phone: [redacted]

Fax: [redacted]

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

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact the PPD medical monitor:

Phone: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (e.g., inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Wayne, PA (USA)
[redacted]

Shire, Basingstoke, Hampshire (UK)
[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS

AAP	American Academy of Pediatrics
ADHD	attention-deficit/hyperactivity disorder
ADHD-RS_IV	attention-deficit/hyperactivity disorder rating scale- IV
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
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
DBP	diastolic blood pressure
DMC	data monitoring committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EC	ethics committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ET	early termination
EU	European Union
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
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
PAPA	preschool age psychiatric assessment
PATS	Preschool ADHD Treatment Study
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
UK	United Kingdom
US	United States
WBC	white blood cell

STUDY SYNOPSIS

Protocol number: SPD489-348	**Drug:** Lisdexamfetamine dimesylate
Title of the study: A Phase 3, Open-label, Multicenter, 12-Month Safety and Tolerability Study of SPD489 in Preschool Children Aged 4-5 Years Diagnosed with Attention-deficit/Hyperactivity Disorder	
Number of subjects: Approximately 100 subjects will be enrolled into this study. Subjects will enroll into this study from antecedent study, SPD489-211 or SPD489-347. If a decision is made to enroll subjects directly, the study procedures and definition of baseline for directly enrolled subjects will be described in the amended protocol. The sample size was established to provide long-term safety data in this population.	
Investigator(s): Multicenter	
Site(s) and Region(s): Approximately 20 sites in the United States (US)	
Study period (planned): 2014-2021	**Clinical phase:** 3
Objectives: **Primary:** To evaluate the long-term safety of SPD489 administered as a daily morning dose (5, 10, 15, 20, and 30mg/day) in preschool children (4-5 years of age inclusive) diagnosed with Attention-deficit/Hyperactivity Disorder (ADHD). The evaluation of safety and tolerability will be based on the occurrence of treatment-emergent adverse events (TEAEs), specific evaluation of blood pressure, pulse, weight, height, clinical laboratory evaluations, electrocardiogram (ECG) results, and sleep assessments. **Secondary:** 1. To describe the long-term efficacy of SPD489 using the clinician administered Attention-deficit/Hyperactivity Disorder Rating Scale-IV Preschool Version (ADHD-RS-IV Preschool Version). 2. To describe the long-term efficacy of SPD489 using global clinical measures of improvement, as measured by the Clinical Global Impressions – Global Improvement (CGI-I).	
Rationale: The purpose of the study is to evaluate the long-term safety of SPD489 in preschool children who are diagnosed with ADHD. 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, along 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 long-term safety data in this population will provide important information on the use of SPD489 in the preschool ADHD population.	

Investigational product, dose, and mode of administration:

The sponsor will provide SPD489 as 5, 10, 15, 20, and 30mg strength capsules.

All subjects will be instructed to take 1 capsule daily throughout the study at approximately 7:00AM (+/-2 hours). SPD489 will be administered one of the following ways:

- swallow SPD489 capsules whole, or
- open capsules, empty and mix the entire contents either 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 can not be split. The empty gelatinous capsule should be discarded.

Methodology:

This study is a Phase 3 long-term, open-label, safety and tolerability study in preschool children (4-5 years of age inclusive at the time of entry into antecedent study or at the time of enrollment if directly enrolled) with Attention-deficit/Hyperactivity Disorder (ADHD).

The study will enroll two types of subjects; Subjects "A" and Subjects "B". The "A" Subjects will have 2 periods: (1) Dose Maintenance and (2) Safety Follow-up. The "B" Subjects will have 4 periods: (1) Screening and Washout; (2) Dose-optimization; (3) Dose Maintenance; and (4) Safety Follow-up.

The duration of the evaluation phase for "A" Subjects (Dose Maintenance) and "B" Subjects (Dose-optimization and Maintenance) will be 52 weeks.

SPD489 will be provided in 5, 10, 15, 20, and 30mg capsules.

Visit 0 procedures for "A" Subjects will be performed at the final dose maintenance visit of the antecedent study.

Subjects will be required to visit the site up to 20 times over a 57-week period, depending on their assignment. "A" Subjects may visit the site up to 13 times while "B" Subjects may visit the site up to 18 times.

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 male or female aged 4-5 years inclusive at the time of consent for an antecedent SPD489 trial in the preschool ADHD population.
2. For "A" Subjects: Subject is on a known dose of SPD489 and completed the final visit of the treatment phase of an unblinded antecedent study without experiencing any clinically significant adverse events (AEs) that would preclude exposure to SPD489 and can directly enter this study without gap between the antecedent study and this study (defined as ≤3 days since last dose in the prior study), OR

   For "B" Subjects: Subject requires dose titration and completed at least the dose optimization and follow up of a blinded antecedent study without experiencing any clinically significant adverse events (AEs) that would preclude exposure to SPD489, OR

   For "B" Subjects: Subject completed the final visit of the treatment phase of an unblinded antecedent study without experiencing any clinically significant adverse events (AEs) that would preclude exposure to SPD489, and did not enroll in this study within 3 days (i.e. >3 days since last dose in the prior study).
3. Subject's parent or legally authorized representative (LAR) must provide signature of informed consent, and there must be documentation of assent (if applicable) by the subject indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions in accordance with the International Conference on Harmonisation (ICH) GCP Guideline E6 (1996) and applicable regulations, before completing any study-related procedures.
4. Subject and parent/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 same parent/LAR should be available daily to dispense the dose of investigational product for the study duration.
5. For "A" Subjects: Subject has a satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by physical examination findings or vital sign results that would preclude treatment with SPD489.

   For "B" Subjects: Subject has a satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by physical examination findings, clinical laboratory test results, ECG results, or vital sign results that would preclude treatment with SPD489.
6. Subject has lived with the same parent or guardian for ≥6 months.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met at Visit 0 for "A" Subjects or at Screening (Visit -1) and/or Baseline (Visit 0) for "B" Subjects. These criteria apply to all subjects regardless of duration since participation in an antecedent trial:

1. Subject was terminated from an antecedent SPD489 trial for non-compliance and/or experienced a serious adverse event (SAE) or AE resulting in termination from any previous SPD489 trial.
2. Subject experienced any clinically significant AEs in any previous SPD489 trial that, in the opinion of the investigator, would preclude further exposure to SPD489.
3. Subject is required to or anticipates the need to take medications that have central nervous system effects or affect performance, such as sedating antihistamines and decongestant sympathomimetics, or are monoamine oxidase inhibitors. Stable use of bronchodilator inhalers is not exclusionary.
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 condition(s) 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 a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
6. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
7. Subject has a blood pressure measurement ≥95th percentile for age, sex, and height at Visit 0.
8. Subject has a known history of symptomatic cardiovascular disease, 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.
9. Subject has a current diagnosis of adjustment disorder, autism, psychosis, or bipolar disorder.
10. Subject is currently considered at risk for suicide in the opinion of the investigator, has previously made a suicide attempt, or is currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation are not necessarily excluded based on the assessment of the investigator.
11. Subject has a history of seizures (other than infantile febrile seizures) or a current diagnosis of Tourette's Disorder.
12. Subject has a chronic or current tic disorder that is judged by the investigator to be exclusionary.
13. Subject is taking any medication that is excluded per the protocol.
14. For "B" Subjects only: Subject had any clinically significant electrocardiogram (ECG) or clinical laboratory abnormalities at the Screening Visit (Visit -1).
15. For "B" Subjects only: Subject has current abnormal thyroid function, defined as abnormal thyroid stimulating hormone (TSH) and thyroxine (T4) at the Screening Visit (Visit -1) or Visit 0. Treatment with a stable dose of thyroid medication for at least 3 months is permitted.

Maximum duration of subject involvement in the study:

- Planned duration of screening period:

  For "A" Subjects: Visit 0 procedures will be assessed at the final dose maintenance visit of the antecedent study.

  For "B" Subjects: 28 days
- Planned duration of treatment period:

  For "A" Subjects: 52 week period

  For "B" Subjects: 52 week period
- Planned duration of safety follow-up period:

  For "A" Subjects: 7 days

  For "B" Subjects: 7 days

Endpoints and statistical analysis:

Subject Populations

- The Screened Set will consist of all subjects who have signed informed consent.
- The Safety Analysis Set will consist of all subjects 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-dose ADHD-RS-IV Preschool Version Total Score assessment during the study.

Safety Endpoints

Safety assessments include the occurrence of treatment emergent adverse events (TEAEs), specific evaluation of blood pressure, pulse, height, weight, clinical laboratory evaluations and electrocardiogram (ECG) results, and sleep assessments [(including sleep diary data, and Children's Sleep Habits Questionnaire (CSHQ)].

Additional safety rating scales utilized in the study will include:

Columbia Suicide Rating Scale (C-SSRS)- Pediatric/Cognitively Impaired Version

Efficacy Endpoint(s)

The efficacy endpoint is defined as the change from baseline on the clinician-administered ADHD-RS-IV Preschool Version Total Score, where baseline is defined as the baseline from the antecedent study.

The additional efficacy endpoint is the Clinical Global Impression-Improvement Scale (CGI-I): The CGI-I will be used to determine the proportion of subjects with an "improved" measurement. The CGI-I categories of "very much improved" and "much improved" will be classified as "improved" and all other assessed categories are grouped together as "not improved".

Statistical Methodology for Safety Endpoint(s)

Safety analyses will be summarized using the Safety Analysis Set, and presented by treatment group of the antecedent studies and overall for AEs, clinical laboratory results, vital signs, ECGs, CSHQ, and sleep diaries. A listing of the C-SSRS will be provided for subjects with any positive responses.

Statistical Methodology for Efficacy Endpoint(s)

The FAS will be used to report the efficacy data. Descriptive summary statistics will be presented by treatment group of the antecedent studies and overall for the observed efficacy variables. Change from baseline in total score for the ADHD-RS-IV Preschool Version Total Score at each on-therapy treatment visit will be summarized.

The number and proportion of subjects with an "improved" measurement in CGI-I will be reported at each applicable post-dose visit.

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments for "A" Subjects

Period	**Dose Maintenance Period**														**Safety Follow-up**
Visit [a]	**Visit 0** [b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ET**	**Telephone Call**
Assessment Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**53**
Assessment Day	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**371**
Informed consent/assent	✓														
Inclusion/exclusion criteria [c]	✓														
Demographics [d]	✓														
Medical and medication history	✓														
Physical examination	✓														
Vital signs [e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height [f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Body weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 1: Schedule of Assessments for "A" Subjects

Period	**Dose Maintenance Period**														**Safety Follow-up**
Visit [a]	**Visit 0** [b]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/ET**	**Telephone Call**
Assessment Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**53**
Assessment Day	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**371**
Clinical laboratory test[g]	✓						✓							✓	
12 lead ECG[h]	✓			✓			✓			✓			✓	✓	
ADHD RS IV [i]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI I [i]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CSHQ [i]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
C SSRS [j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sleep diary [k]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Suitability of subject to remain in study		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigator dose assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Access IWRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product distributed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

Investigational product returned		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a] Visit Window for Visits 1 6 is ± 2 days, and Visit Window for Visits 7 17 is ±5 days [in reference to the Visit 0 date]; Visit Window for Visit 18 is +5 days; Visit Window for Safety Follow up Telephone call is + 2 days.
[b] Visit 0 is the same day as the End of Study Visit for the antecedent study
[c] Inclusion/exclusion criteria must be reviewed at the Washout Telephone Call and at Visit 0.
[d] Demographic data will be pulled programmatically from antecedent study.
[e] Includes oral or tympanic temperature, sitting blood pressure, pulse, and respiratory rate. Measurement of temperature and respiratory rate will be performed as part of the End of Study Visit of the antecedent study . Measurement of blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using the provided automated cuff. The average of each set of 3 measurements will be used to determine continued participation in the study. Blood pressure, pulse and respiratory rate will be determined after subjects have remained seated for approximately 5 minutes. Refer to Section 4.4.1.
[f] Height to be measured without shoes.
[g] Clinical laboratory tests will include hematology, chemistry, endocrinology, and urinalysis.
[h] A single ECG will be collected at, Visits 0, 3, 6, 9, 12, 15and 18/ET
[i] Scales to be completed by same rater whenever possible.
[j] C SSRS pediatric/cognitively impaired "Since Last Visit" version is completed for all visits. The scale will be compared to the C SSRS pediatric/cognitively impaired "Baseline" from the antecedent study.
[k] Sleep diary to be completed by parent/LAR. Sleep diaries will be dispensed at Visits 0 17 and collected at Visits 1 18.

ADHD RS IV ADHD Rating Scale IV; 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 Pediatric/Cognitively Impaired; ECG electrocardiogram; ET early termination; IWRS Interactive Web Response System

Table 2: Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period											Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit 0[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Informed consent/assent	✓																					
Inclusion/ exclusion criteria [c]	✓	✓	✓																			
Demographics [d]	✓																					
Medical and medication history	✓																					
Physical examination [e]	✓		✓																			
Vital signs [d,f]	✓		✓[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height [d,g]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 2: Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period											Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit 0[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Body weight[d]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory test[d,h]	✓		✓[m]									✓							✓		✓	
12 lead ECG[d,i]	✓		✓[m]	✓	✓	✓	✓	✓	✓		✓			✓			✓			✓	✓	
ADHD RS IV[j]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI I[j]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CSHQ[j]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
C SSRS[k]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sleep diary[l]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 2: Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period												Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit 0[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Suitability of subject to remain in study				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigator dose assessment				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Access IWRS	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product distributed			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigational product returned				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product compliance				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 2: Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period											Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit 0[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2: Schedule of Assessments for "B" Subjects

Period	Screening and Washout			Dose Optimization						Dose Maintenance Period											Safety Follow-up
Visit [a]	-1 (Screening)	Phone Call	Visit 0[b]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18/ET	Telephone Call
Assessment Week	-4 to -1	-1 to 0	0	1	2	3	4	5	6	8	12	16	20	24	28	32	36	40	44	48	52	53
Assessment Day	-28 to -1		0	7	14	21	28	35	42	56	84	112	140	168	196	224	252	280	308	336	364	371

[a] Visit Window for Visits 1 6 is ± 2 days, and Visit Window for Visits 7 17 is ±5 days [in reference to the Visit 0 date]; Visit Window for Visit 18 is +5 days; Visit Window for Safety Follow up Telephone call is + 2 days.
[b] Visit 0 is the same day as the End of Study Visit for the antecedent study
[c] Following successful screening, a study center representative will contact the subject/parent/LAR to provide instruction on discontinuing any prohibited medication for the Washout Period (if applicable). Inclusion/exclusion criteria must be reviewed at the Washout Telephone Call and at Visit 0.
[d] Demographic data will be pulled programmatically from antecedent study.
[e] A physical examination, vital signs, height, weight, clinical laboratory assessments, and ECG are required to be repeated if > 30 days have elapsed since the End of Study visit of the antecedent study. The results must be reviewed by the Investigator prior to the subject being enrolled at (Visit 0).
[f] Includes oral or tympanic temperature, sitting blood pressure, pulse, and respiratory rate. Measurement of temperature and respiratory rate will be performed at the Screening Visit (Visit 1) only. Measurement of blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using the provided automated cuff. The average of each set of 3 measurements will be used to determine continued participation in the study. Blood pressure, pulse and respiratory rate will be determined after subjects have remained seated for approximately 5 minutes. Refer to Section 4.4.1
[g] Height to be measured without shoes.
[h] Clinical laboratory tests will include hematology, chemistry, endocrinology, and urinalysis.
[i] A single ECG will be collected at Screening (Visit 1), Visits 0, 3, 6, 9, 12, 15and 18/ET
[j] Scales to be completed by same rater whenever possible.
[k] C SSRS pediatric/cognitively impaired "Since Last Visit" version is completed for all visits. The scale will be compared to the C SSRS pediatric/cognitively impaired "Baseline" from the antecedent study.
[l] Sleep diary to be completed by parent/LAR. Sleep diaries will be dispensed at Visits 0 17 and collected at Visits 1 18.
[m] An abbreviated physical examination and all clinical laboratory tests must be repeated at Visit 0 if >30 days have elapsed since the Screening Visit. Results must be obtained and reviewed prior to determining eligibility.
ADHD RS IV ADHD Rating Scale IV; 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 Pediatric/Cognitively Impaired; ECG electrocardiogram; ET early termination; IWRS Interactive Web Response System

1. BACKGROUND INFORMATION

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

SPD489 capsules contain 5, 10, 15, 20, or 30mg 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: dextro (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 CNS by increasing the availability of naturally occurring amines that have important functions in nerve terminals. Amphetamine increases synaptic levels of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) through multiple mechanisms (Hardman et al. 2001). It promotes the release of DA, NE, and 5-HT into the extraneuronal space, and also inhibits the reuptake of DA and NE 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 SBP and DBP, 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 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 has become clear 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 PAPA, 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 2004; Greenhill 2008). In 2007, the National Survey of Children's Health obtained information from parents of 73,123 children aged 4-17 years (MMWR 2010). Parents reported a current diagnosis of ADHD in 5.5% of 4-10 year olds (MMWR 2010). Prevalence in males aged 4-11 is roughly 3 times greater than in females (Szatmari 1989).

Attention-deficit/hyperactivity disorder is characterized by symptoms of inattention, hyperactivity, and impulsivity that are "maladaptive and inconsistent with developmental level" (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 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 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 PAPA and the 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; Connor et al. 2003). In a longitudinal study which followed children from ages 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).

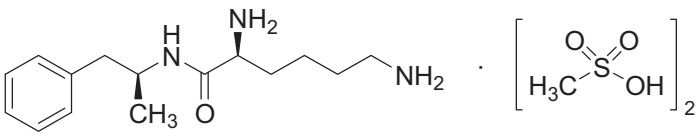
Currently, the lack of a robust body of evidence derived from controlled clinical studies in preschool children makes it difficult to create reliable treatment recommendations. The AAP ADHD Clinical Practice guideline suggests that preschool children with ADHD initiate treatment with behavioral therapy prior to using pharmacotherapy (Subcommittee on ADHD 2011); however the PATS results indicates that (13%) 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 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. Clearly, 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*-[(1*S*)-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 investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, 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 intra-subject and inter-subject 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 $t_{½}$ 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 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 (e.g., 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 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, along 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).

Generating long-term safety data in this population will provide important information on the use of SPD489 in the preschool ADHD population.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of this study is to evaluate the long-term safety of SPD489 administered as a daily morning dose (5, 10, 15, 20, and 30mg/day) in preschool children (4-5 years of age inclusive) diagnosed with ADHD.

The evaluation of safety and tolerability will be based on the occurrence of TEAEs, specific evaluation of blood pressure, pulse, weight, height, clinical laboratory evaluations and ECG results, and sleep assessments.

2.2.2 Secondary Objectives

- To describe the long-term efficacy of SPD489 using the clinician-administered Attention-deficit/Hyperactivity Disorder Rating Scale-IV Preschool Version.
- To describe the long-term efficacy of SPD489 using global clinical measures of improvement, as measured by the CGI-I.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

Approximately 100 subjects will be enrolled in this long-term, open-label study to evaluate safety and tolerability of SPD489, administered as a daily morning dose in the treatment of children 4-5 years of age with ADHD. SPD489 will be provided in 5, 10, 15, 20, and 30mg capsules.

This study will enroll subjects who participated in an antecedent SPD489 study (SPD489-211 or SPD489-347). Subjects entering into this study will be classified as either an "A" Subject or a "B" Subject, determined by the need to retitrate the SPD489 dose, defined as follows:

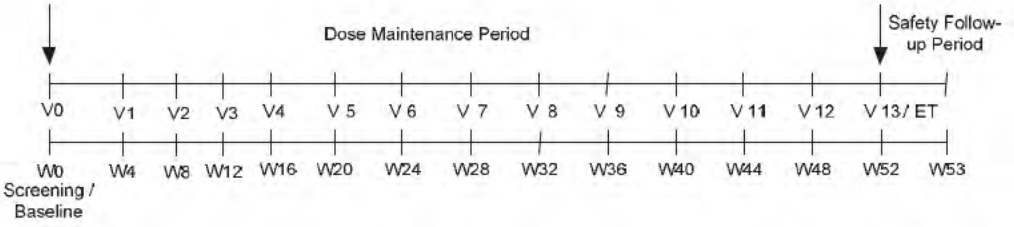
- "A" Subjects are subjects on a known dose of SPD489, classified as subjects who completed the final visit of the treatment phase of an unblinded antecedent study (SPD489-211) who are directly entering this study ≤3 days after the last dose of study medication in the previous study.
- "B" Subjects are subjects who require dose titration, classified as subjects who completed at least the dose optimization and follow up of the blinded antecedent study (SPD489-347) OR those subjects who completed the final visit of the treatment phase of the unblinded antecedent study (SPD489-211) and did not enroll in this study within 3 days.

For "B" Subjects, screening assessments (physical examination, vital signs, height, weight, clinical laboratory tests, and ECGs) must be repeated for this study if more than 30 days have elapsed since the conclusion of the antecedent study.

During the Dose Maintenance Period for both "A" and "B" Subjects, the investigator may make further dose adjustments based upon TEAEs and clinical judgment.

The Study design that "A" Subjects will follow consists of up to 2 periods: Dose Maintenance and Safety Follow-up. These subjects will be required to visit the site up to 14 times over a 53-week period. W0 Baseline procedures will be assessed at the final dose maintenance visit of the antecedent study. The study design is demonstrated below in Figure 2:

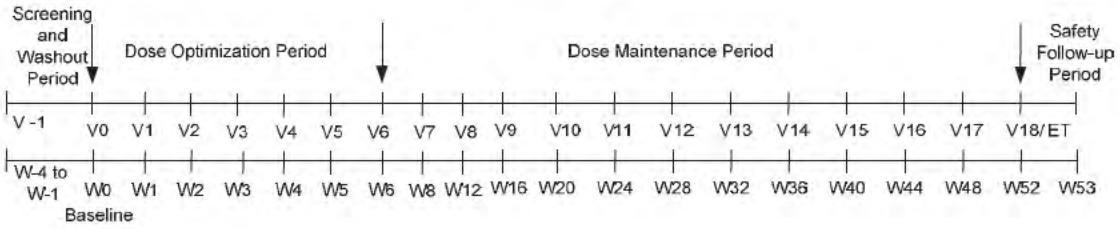
Figure 2: Study Design Flow Chart for "A" Subjects



ET early termination; V visit; W week.

The Study design that "B" Subjects will follow consists of up to 4 periods: Screening and Washout, Dose Optimization, Dose Maintenance, and Safety Follow-up. These subjects will be required to visit the site up to 20 times over a 57-week period. The study design is demonstrated below in Figure 3:

Figure 3: Study Design Flow Chart for "B" Subjects



ET early termination; V visit; W week.

3.2 Duration and Study Completion Definition

The duration of the evaluation phase for "A" Subjects (Dose Maintenance and Safety Follow-up) will be 53 weeks, while the duration for "B" Subjects (Dose Screening & Washout, Dose Optimization, Dose Maintenance, and Safety Follow-up) will be 57 weeks. The subject's maximum duration of participation is expected to be approximately 399 days. The study will be completed in approximately 36 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 approximately 20 sites in US.

4. STUDY POPULATION

Each subject/parent or LAR must participate in the informed consent process and provide written informed consent/assent 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 male or female aged 4-5 years inclusive at the time of consent for an antecedent SPD489 trial in the preschool ADHD population.
2. For "A" Subjects: Subject is on a known dose of SPD489 and completed the final visit of the treatment phase of an unblinded antecedent study without experiencing any clinically significant AEs that would preclude exposure to SPD489 and can directly enter this study without gap between the antecedent study and this study (defined as ≤3 days since last dose in the prior study), OR

   For "B" Subjects: Subject requires dose titration and completed at least the dose optimization and follow up of a blinded antecedent study without experiencing any clinically significant AEs that would preclude exposure to SPD489, OR

   For "B" Subjects: Subject completed the final visit of the treatment phase of an unblinded antecedent study without experiencing any clinically significant AEs that would preclude exposure to SPD489, and did not enroll in this study within 3 days (i.e., >3 days since last dose in the prior study).
3. Subject's parent or LAR must provide signature of informed consent, and there must be documentation of assent (if applicable) by the subject indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions in accordance with the ICH GCP Guideline E6 (1996) and applicable regulations, before completing any study-related procedures.
4. Subject and parent/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 same parent/LAR should be available to dispense the dose of investigational product for the study duration.

5. For "A" Subjects: Subject has a satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by physical examination findings or vital sign results that would preclude treatment with SPD489.

   For "B" Subjects: Subject has a satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by physical examination findings clinical laboratory test results, ECG results, or vital sign results that would preclude treatment with SPD489.

6. Subject has lived with the same parent or guardian for ≥6 months.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria are met at Visit 0 for "A" Subjects or at Screening (Visit -1) and/or Visit 0 for "B" Subjects. These criteria apply to all subjects regardless of duration since participation in an antecedent trial.

1. Subject was terminated from an antecedent SPD489 trial for non-compliance and/or experienced a SAE or AE resulting in termination from any previous SPD489 trial.
2. Subject experienced any clinically significant AEs in any previous SPD489 trial that, in the opinion of the investigator, would preclude further exposure to SPD489.
3. Subject is required to or anticipates the need to take medications that have central nervous system effects or affect performance, such as sedating antihistamines and decongestant sympathomimetics, or are monoamine oxidase inhibitors. Stable use of bronchodilator inhalers is not exclusionary.
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 condition(s) 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 a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
6. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
7. Subject has a blood pressure measurement ≥95th percentile for age, sex, and height at Visit 0.
8. Subject has a known history of symptomatic cardiovascular disease, 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.

9. Subject has a current diagnosis of adjustment disorder, autism, psychosis, or bipolar disorder.
10. Subject is currently considered at risk for suicide in the opinion of the investigator, has previously made a suicide attempt, or is currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation are not necessarily excluded based on the assessment of the investigator.
11. Subject has a history of seizures (other than infantile febrile seizures) or a current diagnosis of Tourette's Disorder.
12. Subject has a chronic or current tic disorder that is judged by the investigator to be exclusionary.
13. Subject is taking any medication that is excluded per the protocol.
14. For "B" Subjects only: Subject had any clinically significant ECG or clinical laboratory abnormalities at the Screening Visit (Visit -1).
15. For "B" Subjects only: Subject has current abnormal thyroid function, defined as abnormal TSH and T4 at the Screening Visit (Visit -1) or Visit 0. Treatment with a stable dose of thyroid medication for at least 3 months is permitted.

4.3 Reproductive Potential

4.3.1 Female Contraception

Contraception is not applicable as 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 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 (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for the Safety/Follow-up visit 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, date of stopping investigational product, and the total amount of investigational product taken must be recorded in the CRF and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Management of Blood Pressure and Pulse During the Study

To ensure that potential blood pressure and pulse increases associated with the use of SPD489 in this population are carefully monitored and appropriately managed, all subjects 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 for Health Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (2005).

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 >15mmHg from Visit 0 was selected for this protocol.

If there are elevations in the average (of 3 readings with approximately 2 minutes between readings) systolic and/or diastolic blood pressure based on the criteria defined below further assessment will be required:

- Elevations in average (of 3 readings) sitting systolic blood pressure defined as an increase of >15 mmHg from Visit 0 of the antecedent study for “A” Subjects or Visit 0 for “B” Subjects or an average (of 3 readings) sitting systolic blood pressure value ≥95th percentile for age, sex, and height percentile
- Elevations in average (of 3 readings) sitting diastolic blood pressure defined as an increase of >15 mmHg from Visit 0 of the antecedent study for “A” Subjects or Visit 0 for “B” Subjects or an average (of 3 readings) sitting diastolic blood pressure value ≥95th percentile for age, sex, and height percentile

The investigator will discuss each subject meeting any criterion with the medical monitor, and a joint decision between the investigator and the medical monitor will be made regarding dose reduction and continued participation in the study. If the dose has been previously decreased, or if the subject is already at the lowest dose, then the subject will be immediately discontinued from the study.

If the subject is allowed to remain in the study, an unscheduled visit will be conducted the next business day. If a visit cannot be conducted the next day, the subject may be discontinued from the study.

At the unscheduled visit, 3 individual measurements will be obtained and the average of the 3 blood pressure measurements for each parameter will be reported. The investigator will notify the medical monitor of the results and if the previously met criteria remain, the subject will be discontinued from the study.

Any subject with a systolic or diastolic blood pressure measurement <95th percentile for age, sex, and height percentile may be discontinued from the study based upon the clinical judgment of the investigator regarding the subject's safety.

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 Reports "Resting Pulse Rate Reference Data for Children, Adolescents, and Adults: United States, 1999-2008."

Elevations in the average (of 3 readings) sitting pulse, defined as 126 beats per minute (bpm) - equivalent to the 99th percentile for this age range, require further assessment.

The investigator will discuss each subject meeting this criterion with the medical monitor, and a joint decision between the investigator and the medical monitor regarding dose reduction and continued participation in the study. If the dose has been previously decreased, or if the subject is already at the lowest dose, then the subject will be immediately discontinued from the study.

If the subject is allowed to remain in the study, an unscheduled visit will be conducted the next business day. If a visit cannot be scheduled the next day, the subject must be discontinued from the study.

At the unscheduled visit, the investigator will notify the medical monitor of the result and if the pulse is still >126 bpm, the subject will be discontinued from the study.

Any subject with a pulse rate ≤126 bpm may be discontinued from the study upon the clinical judgment of the investigator regarding the subject's safety.

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/LAR
- Lost to follow-up
- Lack of efficacy
- Blood pressure and/or pulse criteria met
- Other (must be specified).

4.4.3 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent or LAR of any subject 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 since the subject's last visit in the antecedent study 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.

Washout for all prior medications must be a minimum of 5 times the half-life of the medication.

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 permitted during the study are listed below:

- Stable dose of thyroid medication, provided the same dose had been used during the antecedent study Stable 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
- 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 3 details the washout period, relative to Visit 0, for treatments that are excluded during this study. Subjects can only be instructed to discontinue a medication for this study after the informed consent has been obtained.

Table 3: Common Excluded Treatments and Associated Washout Period– Relative to Visit 0-

	Minimum Number of Days Before Visit 0		
Treatment	**7**	**14**	**30**
Psychostimulants, Amphetamines, and Amphetamine-like agents	X		
Antihypertensives [a]	X		
Antihistamines (centrally and peripherally-active)		X	
Herbal preparations (including melatonin)		X	
Investigational compounds (other than the investigational compound received during participation in 1 of the respective antecedent SPD489 studies).			X
Sedatives, anxiolytics, antipsychotics [a]			X
Monoamine oxidase inhibitor (MAOIs) [a]			X
Antidepressants [a]			X
Clonidine and guanfacine			X
Selective noradrenaline reuptake inhibitors and noradrenaline reuptake inhibitors [a]			X

Table 3: Common Excluded Treatments and Associated Washout Period– Relative to Visit 0-

	Minimum Number of Days Before Visit 0		
Treatment	**7**	**14**	**30**

[a] 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, 15, 20, and 30mg capsules. Additional information is provided in the current SPD489 IB.

6.1.1 Blinding the Treatment Assignment

Not applicable.

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

All subjects will receive open-label SPD489 during this study.

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

6.2.3 Dosing

Dosing should begin at approximately 7:00AM (+/-2 hours) on the morning after 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 will be administered one of the following ways:

- swallow SPD489 capsule whole, or
- open capsule, empty and mix the entire contents with either yogurt, water or orange juice.

The contents should be mixed until completely dispersed. The subject must ingest the entire amount of 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.

A subject from the open-label antecedent study (SPD489-211) will enter this study on their optimal dose, if entering this study within 3 days. However, if a subject is entering this study from the double-blind antecedent study (SPD489-347), or the subject does not immediately enter following the dose maintenance period of the unblinded study (SPD489-211), then the subject will begin dosing at 5mg of SPD489 and should be titrated in a stepwise fashion until an optimal dose is reached.

The objective of dose optimization during the first 6 weeks for "B" Subjects is to ensure that subjects are titrated to an optimal dose of study drug based on TEAEs and clinical criteria.

The Investigator will categorize subject response into 1 of the 3 conditions, along with the associated actions, below. Dose optimization should continue during the first 4 weeks until an "acceptable response" is achieved.

- **Intolerable response** (i.e., subject experiences intolerable side effects): This response suggests tapering the subject to a lower dose of investigational product (if available). However, if this lower dose also produces an intolerable effect, the subject should be discontinued from the study.
- **Ineffective response** (i.e., subject has not achieved at least a 30% reduction in ADHD-RS-IV Preschool Version Total Score from Baseline (Visit 0) of the antecedent study and a CGI-I score of 1 or 2): This response suggests titrating the subject to the next available dose of investigational product (if available, provided there are no tolerability issues).
- **Acceptable response** (i.e., subject has achieved at least a 30% reduction in ADHD-RS-IV Preschool Version Total Score from Baseline (Visit 0) of the antecedent study and a CGI-I score of 1 or 2 with tolerable side effects): This response suggests that an optimal dose has been achieved and the subject should maintain this dose for the remainder of the study.

Further, if the "acceptable" dose is well tolerated and, in the opinion of the clinician, the subject may potentially receive additional symptom reduction, the dose may be increased to the next dose strength.

Dosing will continue at the protocol specified doses of 5, 10, 15, 20, and 30mg for all subjects for the duration of the trial. Subjects who turn 6 years old during the course of the trial will be expected to remain on a protocol specified dose. Higher doses of SPD489, consistent with the approved product labeling for children ages 6 and older will not be provided as part of this protocol. If the Investigator believes a subject who turns 6 during the course of the trial requires a higher dose of SPD489, the subject must be discontinued from the trial.

Investigators have the option to down-titrate a subject in the event the dose is not tolerated. If the subject experiences unacceptable tolerability on the 5mg dose, the subject will be discontinued. Additionally, the Investigator should not decrease or increase the dose by more than 1 dose level at any 1 visit. During the Maintenance Period, the investigator may make further dose adjustments based upon TEAEs and clinical judgment.

Subjects who are unable to tolerate investigational product will be discontinued.

6.2.4 Unblinding the Treatment Assignment

Not applicable.

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 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 (e.g., 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 9-count and 30-count high density polyethylene bottles with child-resistant closures.

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 (i.e., 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), e.g., 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 (e.g., 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.

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 (i.e., 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 (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated 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:

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

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 and Table 2) 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 i.e., ADHD-RS-IV Preschool Version, CGI-S, CGI-I, CSHQ and Columbia Suicide Rating Scale (C-SSRS)

Pediatric/Cognitively Impaired Version must be completed by the same rater whenever possible.

For "A" Subjects, throughout the Dose Maintenance Period of the study, visits should be scheduled as outlined (±5 days) with reference to Visit 0. The Follow-up Telephone Call should be scheduled 7 days post-last dose with a +2 day visit window.

Subjects will be required to visit the site up to 14 times over a 53-week period.

For "B" Subjects, throughout the Dose-Optimization Period of the study, visits should be scheduled as outlined (±2 days), and throughout the Dose-Maintenance Period of the study, visits should be scheduled as outlined (±5 days) with reference to Visit 0. The Follow-up Telephone Call should be scheduled 7 days post-last dose with a +2 day visit window.

Subjects will be required to visit the site up to 20 times over a 57-week period.

Additional unscheduled visits and/or assessments may occur as needed for safety (e.g., 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/LAR prior to any study-related procedures conducted during the Screening Visit (Visit -1). There must also be documentation of assent (if required by 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 (see Table 2). A subject cannot be instructed to wash out any medication for this study until after informed consent is obtained.

Screening assessments may take place across multiple days to allow enough time to complete all procedures and confirm initial study eligibility. Screening procedures and dates should be well documented in the source documents and CRF. The screening date is the date the parent/LAR has signed informed consent for this study. Subjects requiring washout must have an abbreviated physical examination, clinical laboratory tests, and 12-lead ECG repeated if more than 30 days have elapsed since the safety measurements at the Screening Visit (Visit -1) were collected.

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 administered investigational product.

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) for "B" Subjects

All "B" Subjects will be screened at Visit -1 to establish eligibility for study participation. Some screening assessments (vital signs, height, weight, clinical laboratory tests, and ECGs) must be repeated if more than 30 days have elapsed since the End of Study Visit of the antecedent study.

Table 2 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:

- All AEs occurring after signature of informed consent must be recorded in the source documents and CRF. Any AE ongoing at the time of the End of Study Visit from the antecedent study must be recorded on the CRF for this study.
- Document any new findings on the Medical History CRF with enough detail to permit detection of change over time.
- 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 CRO Medical Monitor, will confirm the subject's eligibility to participate in this study.
- Blood pressure and pulse will be collected 3 times (with approximately 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).
- The "Since Last Visit" 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).

7.1.1.2 Washout Telephone Call (Visit Phone Call) for "B" Subjects

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.

All "B" Subjects requiring washout must have an abbreviated physical examination, clinical laboratory tests, and 12-lead ECG repeated if more than 30 days have elapsed since these safety measurements at the Screening Visit (Visit -1) were collected. The results of these assessments must be reviewed by the Investigator prior to the subject being enrolled.

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

- Schedule Visit 0
- Review the inclusion/exclusion criteria
- Ask about any concomitant medications that the subject is taking. If any concomitant medications that require washout are noted, instructions for appropriate washout should be provided
- 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 Visit 0 for "A" Subjects

Visit 0 for "A" Subjects is the same day as the End-of-Study Visit for the antecedent study. Subjects will be screened for eligibility for the SPD489-348 during this visit.

The Principal Investigator or his/her designee must obtain written informed consent from the subject's parent/LAR prior to any SPD489-348 study-related procedures conducted during Visit 0. There must also be documentation of assent (if required by 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 SPD489-348 study-related procedures.

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

Table 1 outlines all procedures to be conducted during Visit 0 with further clarification provided below:

- Blood pressure and pulse will be collected 3 times (with approximately 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).
- For eligible subjects, the investigator or assigned study center staff designee will access the IWRS to enroll the subject and obtain an investigational medicinal 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 Visit 0.
- The C-SSRS "Since Last Visit" Version of the Pediatric/Cognitively Impaired Version should be completed.

7.1.1.4 Visit 0 for "B" Subjects

Once all screening results, including clinical laboratory tests and ECGs, have been obtained in addition to repeat assessments (if required), and reviewed and after the subject has completed any required washout period (if applicable), subjects will return to the study center for their Visit 0.

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

Table 2 outlines all procedures to be conducted during 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 and clinical laboratory tests must be repeated, and the results reviewed by the Investigator prior to the subject being enrolled.
- Blood pressure and pulse will be collected 3 times (with approximately 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).
- For eligible subjects, the investigator or assigned study center staff designee will access the IWRS to enroll the subject and obtain an investigational medicinal 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 Visit 0.
- The C-SSRS "Since Last Visit" Version of the Pediatric/Cognitively Impaired Version should be completed.

7.1.2 Treatment Period

7.1.2.1 Dose-optimization Period (Visits 1 to 6) for "B" Subjects

During the first 6 weeks of treatment, visits will be scheduled every 7 days (±2 days) to assess safety, efficacy, and tolerability and to allow investigators to titrate subjects to their optimal dose of SPD489 based on TEAEs and the dosing guidelines in Section 6.2.3.

If the optimal dose is well tolerated and, in the opinion of the investigator, the subject would potentially receive additional symptom reduction, the subject may be titrated to the next allowed dose.

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

See Table 2 for procedures that are completed at Visits 1 to 6. Further clarification for these visits is outlined below:

- At each visit during the Dose-optimization Period, subjects must return any empty or unused bottles to permit drug accountability and compliance to be assessed.
- Subjects will be dispensed a 9-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 approximately 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 whenever possible.
- The sleep diary is to be completed by the parent/LAR.
- The C-SSRS "Since Last Visit" Version of the Pediatric/Cognitively Impaired Version should be completed during the Optimization Period.

7.1.2.2 Dose Maintenance Period (Visits 1 to 13/ET) for "A" Subjects

Following Visit 0 subjects will continue daily morning treatment for an additional 48 weeks. Subjects will attend the clinic every 4 weeks for procedures to be performed.

Throughout the 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 Maintenance Period. Additional clarification on the procedures to be performed during the Maintenance Period is provided below:

- Scales are to be completed by the same rater whenever possible
- At each visit during the Maintenance Period, subjects must return any empty or unused bottles to permit drug accountability and compliance to be assessed.
- Subjects will be dispensed a 35-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 approximately 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 Dose Maintenance Period (Visits 7 to 18/ET) for "B" Subjects

Following titration to an optimal dose of SPD489, subjects will continue daily morning treatment for an additional 48 weeks. Subjects will attend the clinic every 4 weeks for procedures to be performed.

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

Table 2 outlines the procedures to be completed at each visit during the Maintenance Period. Additional clarification on the procedures to be performed during the Maintenance Period is provided below:

- Scales are to be completed by the same rater whenever possible
- At each visit during the Maintenance Period, subjects must return any empty or unused bottles to permit drug accountability and compliance to be assessed.
- Subjects will be dispensed a 35-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 approximately 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).

7.1.2.4 End-of-Study Visit (Visit 13/ Early Termination) for "A" Subjects

All subjects who complete the study or discontinue early will complete the End-of-Study Visit.

Table 1 list the procedures to be completed at Visit 13/ET and should serve as the primary point of reference regarding visit-specific study procedures.

Further clarification on the procedures performed during the End-of-Study Visit is provided below:

- Unused investigational product and empty containers will be collected to calculate medication compliance.
- Blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) during the visit. The average of each set of 3 measurements will be used to determine if additional follow-up is needed (see Section 4.4.1).

7.1.2.5 End-of-Study Visit (Visit 18/ Early Termination) for "B" Subjects

All subjects who complete the study or discontinue early will complete the End-of-Study Visit.

Table 2 list the procedures to be completed at Visit 18/ET and should serve as the primary point of reference regarding visit-specific study procedures.

Further clarification on the procedures performed during the End-of-Study Visit is provided below:

- Unused investigational product and empty containers will be collected to calculate medication compliance.
- Blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) during the visit. The average of each set of 3 measurements will be used to determine if additional follow-up is needed (see Section 4.4.1).

7.1.3 Safety Follow-up Period for "A" and "B" Subjects

The follow-up period for this protocol is 7 days +2 days from the last dose of investigational prodect.

At the end of this period there will be a telephone call initiated by the site to query for any SAE follow-up 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

There is no planned care for subjects after this study. The investigator will discuss the available ADHD treatment options for subjects.

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 and Table 2.

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 and Table 2 for Visit 13/ET or Visit 18/ET and the Follow-up Telephone Call should be completed.

Whenever possible, raters (including parent/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 and Table 2.

7.2.2 Screening Assessments

Not applicable.

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 secondary efficacy measure, is completed by the Sponsor approved clinician at the site and will be administered at Visit 1 and each subsequent visit up to and including the End of Study Visit 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. Since the ADHD-RS-IV Preschool Version 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 delegated vendor.

The title, version, and date of the ADHD-RS-IV Preschool Version used in this study are included in Table 1 and Table 2.

7.2.3.2 Clinical Global Impressions

The 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 Visit 0 of the antecedent study. Ratings will be completed with respect to ADHD symptoms.

At each visit from Visit 1 up to and including Visit 13/ET (for "A" Subjects) and Visit 18/ET (for "B" Subjects), the Investigator will assess the subject's improvement relative to the 3 target areas of improvement recorded at Visit 0 of the antecedent study, on the CGI-I, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The 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 delegated vendor.

The title, version, and date of the CGI-I used in this study are included in Table 1 and Table 2.

7.2.4 Safety

The name and address of each third party vendor (e.g., 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

Any new medical history, i.e., medical conditions, which arose after the recording of the medical history in the antecedent study, should be recorded at Visit 0 for "A" Subjects and Screening Visit (Visit -1) for "B" Subjects.

7.2.4.2 Physical Examination (Including Height and Weight)

A full physical examination will be performed at Visit 0 for "A" Subjects and at the Screening Visit (Visit -1) for "B" Subjects. Additionally, for "B" Subjects, an abbreviated physical examination is required at Visit 0 if more than 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 per local requirements (e.g., 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 for "B" Subjects at 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 (e.g., "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. Any AE ongoing from the antecedent study must be entered. Any AE ongoing from the antecedent study must be recorded on the CRF for this study. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

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) for "B" Subjects only. For subjects who enter this study within 7 days of completing the antecedent study, vital signs are collected at the End of Study Visit of the antecedent study.

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 seated for a minimum of 5 minutes.

Blood pressure will be determined by automated cuff (the same unit 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 the unit provided by the central ECG vendor. The automated cuff will obtain 3 measurements 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 each visit for all subjects. 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 for "A" Subjects will be performed at Visit 0, Visit 6, and Visit 13/ET. While the Clinical Laboratory assessments for "B" Subjects will be performed at the Screening Visit (Visit -1), Visit 9, Visit 16, and Visit 18/ET. Additionally, clinical laboratory tests are required to be repeated prior to 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.

The following clinical laboratory assessments will be performed:

Biochemistry and Endocrinology

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

Total Cholesterol	Calcium
AST	Uric Acid
Phosphorus	Blood Urea Nitrogen
ALT	Total Bilirubin
Sodium	Creatinine
ALP	Glucose
Potassium	Albumin
GGT	Total Protein
TSH	Lactate Dehydrogenase
Free T4	

Hematology

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

Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
RBC	Monocytes
Platelet count	Eosinophils
WBC count total and differential	Basophils
MCH	Bands
MCHC	MCV

Urinalysis

A urine sample (~10mL) 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 RBC, WBC, casts, and bacteria.

7.2.4.7 Electrocardiogram

For "A" Subjects a 12-lead ECG will be performed at Visit 0, Visit 3, Visit 6, Visit 9, Visit 12 and Visit 13/ET. For "B" Subjects a 12-lead ECG will be performed at the Screening Visit (Visit -1), Visit 0, Visit 1-6, and Visit 8, Visit 11, Visit 14, Visit 17, and Visit 18/ET. Additionally, for "B" Subjects, a 12-lead ECG is required to be repeated prior to Visit 0 with results reviewed before enrolling the subject in the study if more than 30 days have elapsed since the 12-lead ECG completed as part of the Screening Visit (Visit -1) was performed. Additional ECGs may be performed during the study at the Investigator's discretion.

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 to ensure the safety of each subject. An ECG tracing will then be evaluated by a cardiologist at a central ECG reading vendor and returned to the site with a determination of normal or abnormal. Upon review of the report from this vendor, 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 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 completed at every visit to the site starting with the Screening Visit (Visit -1) for "B" Subjects and Visit 0 for "A" Subjects and will be completed by the subject's parent/LAR.

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

7.2.4.9 Columbia-Suicide Severity Rating Scale- Pediatric/Cognitively Impaired Version

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 self-injurious behavior. There are 8 additional suicidal ideation items and 2 additional suicidal behavior items which are completed in cases of positive responses for other items, as well as 2 items for completed suicide and suicide behavior present during the interview. 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. There are two versions of the C-SSRS:

- The "Baseline" version will be administered at the Screening Visit (Visit -1) for all subjects as part of the antecedent study visit procedures.
- The "Since Last Visit" version will be completed for all subjects at each visit in this study.

The title, version, and date of the C-SSRS "Baseline" version and the C-SSRS "Since Last Visit" version used in this study are included in Table 1 and Table 2.

7.2.4.10 Suitability of the Subject to Remain in the Study

At each visit (except for Visit 13/ET or Visit 18/ET) starting with the Visit 1, the Investigator or a medically qualified designee should assess whether it remains in the best interest of the subject to continue in the study and that it is safe for the subject to do so. As part of the assessment of the subject's suitability to remain in the study the Investigator should 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. The Investigator should also ensure that there is appropriate documentation of this assessment in the subject's source notes. 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 an assessment of the subject's 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.

The Investigator should pay particular attention to:

- Any "yes" response to items 2, 3, 4, or 5 on the C-SSRS or any suicidal behavior.

Any subject who has 1 or more positive responses must undergo further evaluation to ensure that they are not in any way at risk. The evaluation and decision should also be clearly documented in the subject's source notes.

7.2.5 Volume of Blood to be Drawn From Each Subject

Table 4: Volume of Blood to be Drawn From Each Subject

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

[a] Biochemistry and hematology clinical laboratory tests will be repeated at Baseline if 30 days or longer have elapsed since the Screening Visit.

During this study, it is expected that approximately 18mL 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 18mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

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

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 pre-treatment 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 (e.g., 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 (e.g., 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 30mg 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 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/legally-authorized representative/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 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 Time Frame

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 and the CRO/Shire Medical Monitor 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 (i.e., 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

Not applicable.

9.4 Statistical Analysis Process

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

The 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® (SAS Institute, Cary, NC 27513).

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

There is no planned interim analysis or adaptive design for this study.

A DMC will be involved in the management of this study. The purpose of the DMC is to monitor safety and tolerability of the investigational product and to protect the interests of patients in the study and of those still to be entered. Data will be provided to the DMC by an independent statistical and reporting group not assigned to the study. The data provided to the DMC will not be considered 'clean' until the database is locked.

Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

9.6 Sample Size Calculation and Power Considerations

Approximately 100 subjects will be enrolled into this study to ensure that at least 50 subjects are exposed to SPD489 for one year. Subjects will enroll directly into this study from an antecedent SPD489 study (SPD489-211 or SPD489-347).

The sample size for this study is not based on statistical considerations.

9.7 Study Population

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

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

The **FAS** will consist of all subjects in the Safety Set who have at least 1 post-dose ADHD-RS-IV Preschool Version Total Score assessment during the study.

9.8 Efficacy Analyses

The FAS will be used to summarize the efficacy data.

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

9.8.1 Clinician-administered ADHD-RS-IV Preschool Version

The efficacy endpoint for the ADHD-RS-IV Preschool Version is defined as the change from baseline on the clinician-administered ADHD-RS-IV Preschool Version Total Score, where baseline is defined as the baseline from the antecedent study for all subjects.

The observed and change from baseline ADHD-RS-IV Preschool Version Total Score will be summarized at each applicable visit using the number of subjects, mean, standard deviation, median, minimum, and maximum values.

9.8.2 Clinical Global Impressions

The efficacy endpoint for the CGI-I is defined as the proportion of subjects who had an "improved" CGI-I measurement. The CGI-I categories of "very much improved" and "much improved" will be classified as "improved" and all other assessed categories will be grouped together as "not improved".

The observed dichotomized CGI-I values will be summarized at each applicable visit using number of subjects and percentages.

9.8.3 Exploratory Efficacy Endpoints

Not applicable.

9.9 Safety Analyses

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

Safety analyses will be presented by treatment group of the antecedent studies and overall for the occurrence of TEAEs, clinical laboratory results, vital signs, ECG results, and sleep assessments including sleep diary data and CSHQ.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class and, by preferred term. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by visit and overall. Potentially clinically important findings will also be summarized or listed.

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

The C-SSRS data will be listed for all subjects with any positive response.

9.10 Other Analyses

No other analyses are planned in this study.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

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

10.1 Sponsor's Responsibilities

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), EU Directive 2001/20/EC, 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), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources 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 sub-investigators 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), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

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 clinical research associate 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 sleep 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 (e.g., 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 (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) 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, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, 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, biohazardous material, or substances for infectious diseases, 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. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is

requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject 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 (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative, 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/legally-authorized representative/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 (i.e., 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

For sites outside the EU, 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.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies the coordinating principal investigator or sponsor, according to national provisions.

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.

For sites outside the EU, 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; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies the coordinating principal investigator, according to national provisions. 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 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 representatives 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 and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., 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 and dates of birth 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 (e.g., 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 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	21 Oct 2014	US

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 BLOOD PRESSURE LEVELS FOR BOYS BY AGE AND HEIGHT PERCENTILES

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 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

APPENDIX 2.3 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 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

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	Baseline Since Last Visit	Baseline 1/14/09 Since Last Visit 1/14/09
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.